LECTURES ON DIGESTION.

LECTURES ON DIGESTION:

AN INTRODUCTION TO THE CLINICAL STUDY OF

DISEASES OF THE DIGESTIVE ORGANS.

Twelve Lectures,

DELIVERED TO PRACTITIONERS AND ADVANCED STUDENTS OF MEDICINE DURING THE WINTER SESSION 1878-9.

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TO

PROFESSOR FRIEDRICH THEODOR FRERICHS,

AS A MARK OF

HIS MOST GRATEFUL ESTEEM,

FROM

THE AUTHOR.

PREFACE.

THE title of this book indicates its origin and purpose. I complied with a request frequently made to me, by publishing these Lectures, which were delivered to physicians in this city during the winter session of 1878-79. The physiology of Digestion in the last few years has presented us with an abundance of new facts, which, from their bearing upon digestive derangements, demand our closest attention, but hitherto they have received no general description. The splendid account of the "Digestion and Absorption of Food," in the second part of Hoppe-Seyler's Physiological Chemistry, stops short at the standpoint of the chemist and of the text-books. In the following Lectures the interests of physicians and clinicists receive the first consideration, and the arrangement and treatment of the subject-matter are from their point of view. I have endeavoured to be as concise in style as possible, avoiding diffuseness, repetition and oratorical digression.

During the last few years I have repeatedly performed

many of the experiments belonging to this subject, but in the following Lectures I have only quoted them where I wished to strengthen statements which hitherto had found no express confirmation, or to appeal to my own experience in disputed questions.

An account of the experiments, with other observations, is given in the Appendix.

I have most willingly consented to Dr. Saundby's desire to translate these Lectures. I am much indebted to him for his elegant and correct translation, and I wish only to add that I have revised the proofs and supplemented the original text by additions from the most recent publications.

C. A. EWALD.

TRANSLATOR'S PREFACE.

No apology is needed for presenting Dr. Ewald's admirable Lectures to English readers. My object has been as far as possible to preserve their individuality, while clothing them in another language.

ROBERT SAUNDBY.

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LECTURES ON DIGESTION.

LECTURE I.

Gentlemen,—More than anywhere else, in diseases of the digestive organs it is possible to avert permanent injury, and to carry out rational and successful therapeutics, by clear and just appreciation of physiological processes. Digestion is comparable to a complicated clock-work, the derangements of which are readily shown by the movements of the hands, but the causes of which are difficult to discover, from the complexity and concealed position of the movement. Therefore the pathology of digestion requires a well-grounded knowledge of the complex processes which effect the transformation of our food into chyle.

This is so plain as scarcely to need to be referred to, as it is unintelligible how any one could come to any conclusion as to the causes of defective action in a clock from inspecting the hands, instead of looking at the works. Such superficial inquiry could only lead to blunders.

But the physiology of digestion has during recent years developed as scarcely any other branch of the subject has done, both in breadth and depth, and a notable list of new observations and brilliant discoveries give it quite another aspect to that which it possessed fifteen or twenty years ago. A great mass of histological and physiological details which teach us the intimate nature of special processes, and the discovery of chemical facts which have led to the attainment of new general points of view, have much elucidated its aspect, filled up many gaps, and turned the current of investigation into quite new channels.

The classical works of Tiedemann, Gmelin, Frerichs, Bidder and Schmidt, stand out as landmarks and indications of the contemporary position of science; but the task belongs to me to follow its development from their time to our own. This is a protracted task, owing to the condition of our literature, as the information is scattered through a hundred monographs, periodicals and reviews. In order that I may give the desired attention to our recent knowledge, and bearing in mind our special object, the relation of derangements of the digestion to our knowledge of the normal processes, I think it best, in the following remarks, to treat chiefly of new facts and theories, and to recapitulate briefly what is generally known, as a sort of foundation on which to place our corner-stone. I am anxious, therefore, in the recital of facts, to speak only of the modus operandi in its grosser features, and to give chemical formulæ and methods only so far as is necessary to make the subject intelligible. On the other hand, I will willingly linger over the clinical aspects whenever a suitable occasion offers for a glance at practical points, and especially from a therapeutic point of view.

In the first place, in the processes going on in the alimentary canal, we have to do with two great groups of matter, organic and inorganic. The latter is taken in the form of water and salts with the food. Water, the importance of

which is too lightly appreciated, quite independent of the fact that it acts as a medium of solution for the different matters in the exchange between the lumen of the alimentary canal and the vessels, in recent times has received new importance from the part it is shown to play in the fermentative processes going on everywhere. The salts undergo certain decompositions according to their affinities, but otherwise suffer no changes. So far as they are soluble in water and diffusible through animal membrane, they are absorbed, turned to account in the organism, and the remainder passed out with the different excretions. So far as they are not soluble, they pass straight through the alimentary canal, and are able, wherever they may lodge, to give rise to mechanical derangements—as, for example, the little soluble phosphate of magnesia frequently forms the nucleus of an intestinal calculus. It is quite otherwise with organic matter. Besides certain organic acids, such as acetic, malic, lactic, butyric, &c., which so far behave like the inorganic, we can recognize three fundamental types under which we may group the most diverse forms and compounds which make up the chaos of our aliment. But the *albuminates*, *carbo-hydrates and fats*, with few exceptions, are not assimilable as such, so that the chief part of the digestive function is the metamorphosis of these into absorbable modifications. The principal means by which the organism performs this duty is by the action of *ferments*. Only by the changes which albumen, fat and starch undergo through these ferments does it happen that they can pass from the intestine into the lacteals: without the action of ferments the nutrition and life of the organism would be impossible. Allow me, therefore, first shortly to sketch the doctrine of ferments and the rôle which they play in the animal organism. They have, at the same time, a general interest not limited to digestion alone, inasmuch as, as has been recently especially indicated by Hoppe-Seyler and Nencki, they take part in the *combustion processes* of the organism.

Lavoisier and Laplace founded on their great discoveries the doctrine of *animal heat as a combustion process*, in which the animal gives out as much heat as it can form by combustion of carbon, which may be found as carbonic acid in the expired air: while Magnus's investigations on the different carbonised and oxidised contents of venous and arterial blood localised this combustion process in the capillaries; so the view stood apparently incontrovertible, that the oxygen taken in by the lungs burns the carbon containing elements of the blood. This process forms in the last instance carbonic acid and water, and, as far as the nitrogenous material is concerned, the products of the so-called retrogressive metamorphosis. This hypothesis seemed so well founded and was so well supported, that, for instance, Liebig believed that on deeper respiration, and consequently increased introduction of oxygen, an immediate increased combustion must ensue, and most physiologists and physicians compared the lungs "to bellows which make a fiercer fire in the forge the more they are blown." But in recent times a reaction has taken place against this long dominant explanation. Pflüger and his school have adopted the view that the cells are, in a certain sense, independent, so far as their function is concerned, of the quantity of oxygen introduced into the blood, somewhat as a mill by the division of the mill-stream must be driven, whether there be more or less water. Then the gas tension of the cells, that is the carbonic acid produced in them by the action of oxygen, increases with their activity, and can, as I have proved, reach its greatest height in fever; on the other hand, chemical facts are known which do not conform to the view that oxidation only goes on in the blood and tissues. The following facts are of this order:—Neither albumen nor fat, under ordinary conditions, as they are present in the blood, can combine with atmospheric oxygen. This occurs only when the oxygen exists as ozone, a body which, as Pflüger, in opposition

to A. Schmidt and Huizinga, has shown, has not yet been proved to be present in the blood. If we extract the oxygen out of the blood into a Torricellian vacuum by an air-pump, at the base of which a slip of guaiacum paper is fastened, no blue colouration occurs, as I have convinced myself in two experiments, following Pokrowsky. Moreover, according to Rajewsky, the friction which the blood undergoes in the capillaries is not sufficient to form ozone, as might be suspected from analogous facts. 2. The relation of the oxygen inhaled to the excreted carbonic acid $\left(\frac{O}{CO_2}\right)$ is, as Voit has found, not always the same under apparently similar conditions, where, according to the combustion theory, we should expect it to be equal. 3. Certain processes go on in the blood which are to be regarded as reduction processes and not oxidations; for instance, the formation of urobilin and bile-colouring matter from the hæmochromogen of the blood corpuscles, the formation of hippuric acid out of quinic acid, and probably of glycogen out of grape sugar, when these substances are introduced into the circulation. 4. Various very easily oxidisable substances, as, for example, pyrogallic acid or pyrocatechin, both derivatives of benzol, probably pass unchanged through the blood, and are excreted in the urine in the form of dichotomised sulphuric acid. For all that, a solution of pyrogallic acid in an alkaline fluid takes up oxygen, and changes with such extraordinary energy that it is employed for the quantitative estimation of this gas in the atmosphere. If we consider these four points, certain comments suggest themselves on the first and second heads. Nothing opposes the supposition that the protein substances, fat, &c., undergo, as the starting-point of the cell activity, a peculiar unknown intramolecular change, which facilitates combustion by the neutral oxygen. As an example of such sudden cell activity, I would quote the play of colours in the pigment cells of many animals, which often depends upon a

sudden re-arrangement or change of the cell contents. What does the second point—Voit's observation—involve? It is, of course, very difficult to have an actual identity of conditions in two separate experiments, which alone would permit a conclusion to be drawn from Voit's figures. The absorption of nutriment, that is, of the material to be burnt, is, as we know, dependent in some measure upon psychical influences even in animals, particularly in such an intelligent animal as the dog; and as these cannot be removed, we must not estimate at too high a value the variations observed in the relation of carbonic acid to oxygen.

On the other hand, both the last points seem to be so important, that I give you the equations according to which these reduction phenomena occur outside the organism in the presence of reducing substances.

1. The reduction of quinic acid to hippuric acid.

Quinic acid + hydriodic acid = benzoic acid + water + iodine.

$$C_7\,H_{14}\,O_6 + 2\,HI = C_7\,H_6\,O_2 + 4\,(H_2\,O) + I.$$

The benzoic acid combines with the glycocoll present in the organism, and forms

Benzoic acid + glycocoll = hippuric acid + water.

$$C_7\,H_6\,O_2 + C_2\,H_5\,NO_2 = C_9\,H_9\,NO_3 + H_2\,O.$$

2. The reduction of the colouring matter of the blood corpuscles, hæmochromogen, into biliary colouring matter and urine colouring matter (bilirubin and urobilin or hydrobilirubin), by the use of nascent hydrogen, a very energetic reducing agent, has been recorded by Hoppe-Seyler.

3. The reduction of grape sugar to glycogen is apparently as follows:

Grape sugar = glycogen + water.

$$C_6\,H_{12}\,O_6 = C_6\,H_{10}\,O_5 + H_2\,O.$$

Phenomena like the preceding, noticed under 3 and 4, are not reconcilable with the view that the elements of the

blood and tissues exclusively support very energetic and rapid oxidising processes. It may, therefore, not seem strange under these circumstances that Hoppe-Seyler should state the course of some processes in animal bodies to be, that "in which the action of water changed organic matter and decomposed it in the same manner as we find it in the process of putrefaction, and can imitate experimentally." Hoppe-Seyler reached this view from the notion that as heat is produced by these processes, and as by the introduction of atomic hydrogen free or nascent oxygen could be given off, strong oxidations (formation of anhydrides, aldehydes, and others, by the simple fermentation of non-derivable bodies) would be made possible. Therefore reduction and oxidation must go on side by side, a process which finds its analogue in numerous chemical reactions.

However, this view is still quite unsupported. The putrefactive processes are provisionally inseparable from the life of the accompanying organism, and what we call putrefaction is a perfectly definite vital process. It cannot advance our knowledge of the subject to apply putrefactive processes to explain vital processes, as each is, after all, only a special form of vital activity. Nevertheless, we may compare these processes with the object of improving our knowledge, and I believe Hoppe's theory should be accepted in this sense. I will therefore adduce facts which are able to further this object very greatly, and also fall into the category of fermentative processes. I shall return to this subject. For the present, it is enough to have drawn your attention to this example, which touches one of the greatest and most important questions in the animal economy, on the bearing of our knowledge of fermentations, quite apart from their relations to zymotic diseases. It is at the same time very interesting that in these doctrines, based on exact data, the vague speculations of earlier times join hands with the more certain acquisitions of advancing knowledge.

The iatro-chemical school, or its head, Van Helmont, in his Ortus Medicinæ, used promiscuously the terms, fermentatio, digestio, putrefactio; Becker thought that combustio and fermentation were analogous processes; Lavoisier compared physiological combustion to the spontaneous burning of dung at lower temperatures; Stevenson derived animal heat from fermentations; and Mitscherlich identified directly life with putrefaction.

The word "ferment" was used by the alchemists of the 14th and 15th centuries in the sense of a force which, without becoming weaker itself, could produce great effects in other masses, a quality which, for example, was sought for in the philosopher's stone. Even in the present day, the definition is current which A. Meyer, a well-known and renowned investigator on this subject, gives in his Chemistry of Fermentation for 1874. It runs thus: "That a number of chemical processes not explicable according to the rule of affinities, owe their occurrence to the presence of certain matter which is not recognisably concerned in the reaction, and the quantity of which stands in inordinately small relation to the magnitude of the chemical processes caused by it." This is, as we shall see further on, not quite exact. But if we keep to the biological standpoint, we may consider it a fact, not quite universal but yet certain, so far as all fermentations in animal bodies are concerned, that fermentations in the presence of water and the ordinary body temperature give rise to extensive chemical processes with the smallest quantity of ferment, processes which without ferments we could only effect by very high temperatures and very energetic oxidising or reducing agents. These processes consist in the decomposition of highly complex compounds into simple molecules with simultaneous increase of water, or, to employ the terms of chemists, *in the hydration of anhydrides.* But this property, which, figuratively speaking, represents in our organism the flame of a Bunsen's burner, which the chemist needs in order to produce similar effects, is that which must

make the activity of ferments appear especially important to us.

Five principal properties are common to all ferments: 1. All ferments belong to organic nature. 2. All ferments act only in the presence of water. 3. The sum of the products contains more hydrogen and oxygen, even in the condition of water, than the original matter. 4. All ferments decompose peroxide of hydrogen. 5. All ferments act best at temperatures between 30° to 35° C. They can endure a temperature of – 20° without injury. Paschutin has proved that the specific action of the salivary ferment remains strong up to 55°, but becomes feebler with higher temperatures, and disappears at 73°.

Thus ferments are not so easily destroyed by heat as was believed at one time. Salkowski has shown that pancreatic ferment may be heated for hours to 160° without losing its specific qualities, and I have recorded the fact that a glycerine extract of stomach and pancreas mixed with water and boiled eighteen minutes, retained its pepsin-forming property. The action of ferments on peroxide of hydrogen is very easy to demonstrate. If we place some commercial peroxide of hydrogen in a test-tube over mercury, and add a few milligrammes of yeast, a development of gas follows very rapidly. This gas is formed by the decomposition of peroxide of hydrogen, and is oxygen in which a glowing match bursts into flame. However, this catalytic property belongs not only to the recognised ferments, but to other compounds, *e.g.* to blood. O. Nasse has observed the destruction of peroxide of hydrogen by many animal organs in different degrees, and refers it to the existence of special and otherwise hypothetical ferments, which effect an important part of the current vital processes in the organs and their elements, the cells. You see how near this view comes to that of Hoppe-Seyler, although reached from another starting-point. On the other hand, it is very interesting that a series of ferment-

ations proceed in the presence of certain substances, in some cases more strongly, in others more feebly, or are quite prevented. This is the case, according to O. Nasse, with a number of neutral salts, which have different influences upon different ferments, such as diastase, saliva ferment, pancreas ferment, &c.; and according to Luchsinger, glycerine injected subcutaneously in great quantities hinders the transformation of liver glycogen into sugar, and prevents the occurrence of artificial diabetes (puncture and curare diabetes). As the action of neutral salts on ferments is not without practical significance, although this indication has not yet been tested, I have reprinted Nasse's table.*

Ferments are the integrated elements of certain vegetable and animal juices and tissues. Their production in a pure condition has extraordinary and hitherto insuperable difficulties, and Hoppe-Seyler has described them shortly "as entirely unknown, quite hypothetical" bodies, which are only known by their actions. But they appear to be allied in their composition to albuminoid bodies. A. Schmidt gives an analysis of the emulsin found in bitter almonds as $C = 48.76$, $H = 7.13$, $N = 14.16$, $S = 1.25$, $O = 18.70$; whilst non-coagulable albumen, according to Dumas and Cahours, has the composition $C = 53.7$, $H = 7.1$, $N = 15.8$, $O + S = 23.6$, $S = 1.8$.

So much for the general properties of ferments.

The references are to authors quoted in the text. The well-known text-books on histology, physiology and physiological chemistry, as well as the monographs of Frerichs, Bidder and Schmidt, Moleschott and others, are not specially indicated.

Hoppe-Seyler. Ueber die Processe der Gährungen und ihre Beziehungen zum Leben des Organismus. Pflüger's Archiv. Bd. xii. Hft. 1.

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Pflüger. Ueber die physiologishe Verbrennung in den lebendigen Organismen. Ibid. Bd. x. p. 251.

* Vide Appendix.

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O. Nasse. Untersuchungen über die ungeformten Fermenten. Pflüger's Archiv. Bd. xi. p. 138.

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LECTURE II.

Gentlemen,—The fact that some fermentations result from animal or vegetable juices and extracts, and others from the functional manifestations of living organisms, has, for a long time, led to their division into organised and unorganised, or, what means the same thing, organic and chemical, direct and indirect ferments. The organised ferments are, so to speak, one with the specific organic structures which we always meet with wherever we find the specific action, and are intimately bound up with the "life" of these structures. The alcoholic ferment is extinguished so soon as the yeast cell is dead. The unorganised ferments are, once existent, independent of the welfare of the mother substance or of the life of their original producers and bearers. Saliva, gastric juice, pancreatic juice, the extracts of certain seeds, as emulsin, myrosin, &c., remain active after the death of the animal or plant. But it is questionable whether this is an essential difference, or only a defect in our knowledge, which does not permit us—to keep to the same example—to extract an alcoholic ferment from yeast, as we extract the gastric ferment from the stomach.

In fact, one consideration favours this. "It is not permissible to identify a ferment, that is to say, a chemical body, which produces decomposition in the fermenting

substance, with the organism in which it is formed" (Hoppe-Seyler); and "nowhere in the whole series of ferment actions does a specially vital process take place, but everywhere only a chemical process." It is obvious that such an explanation, which regards all ferments from a uniform standpoint as secretions of organisms, and allows no direct part in the ferment action to the cell itself, must greatly facilitate our comprehension of these processes. We may hope, sooner or later, to bring about fermentation without these organisms, as we can do now in the case of the "unorganised" ferments. The following considerations support this view: 1. A ferment can be extracted from yeast, which converts lævulose into dextrose, and is called invertin. 2. There is an alcoholic fermentation without anything to do with yeast cells, which at one time were thought to be necessary elements of this process. Lechartier and Bellamy found that chopped-up leaves and fruits of phanerogams formed alcohol without yeast when placed in an atmosphere free from oxygen (carbonic acid). 3. An observation, needing confirmation, of Hoppe-Seyler's, according to which the products of the putrefaction of albumen are given off without the concurrence of bacteria or vibrios, when hydrocele fluid, free from bacteria, is sealed in a glass tube and kept for a week at a temperature of 40°. Also the observations of Paschutin, that butyric fermentation may originate in lactate of lime without special organised ferments, by the addition of animal tissues, skin, intestine, &c. 5. The above-named circumstance that alcoholic fermentation ceases with the death of the yeast, would agree with the existence of a chemical ferment in the yeast cells, if we suppose the latter to be formed continually, but in so small a quantity that it is immediately used up by the fermentation. But, as you perceive, this view is not compatible with the definition of unorganised ferments, according to which the smallest amount can effect the greatest action. Further, the circumstance that the chemical means are at hand to imitate the

action of organised ferments in test-tubes and retorts without their intervention, does not prove that the action of formed ferments must be due to a substance separable from the life and vital functions of the cell, as in the unorganised ferments, and the observations of Lechartier and Bellamy are capable, as we shall see, of another interpretation.

There are, therefore, a series of characteristic differences between the organised and the unorganised ferments. The organised ferments multiply to a certain extent during their activity; the unorganised do not. The organised ferments are, according to a remarkable discovery of P. Bert, killed by oxygen subjected to the compression of many atmospheres; the unorganised remain uninjured. On the other hand, according to Dumas, borax kills invertin, emulsin, myrosin and diastase, while it leaves the alcoholic ferments unaffected. And, finally, all organised ferments require for their origin and the commencement of their activity, as well as for its continuance, the presence of free or combined oxygen; for instance, yeast does so to such a degree that it is able to convert arterial into venous blood; whilst the unorganised ferments, according to Hüfner, can work without any oxygen. The last-named properties do not concern so much the hypothetical ferment as the life of the ferment carrier; but in any case the ferment action comes to an end with the life of the ferment carrier. But this is a point which we are not at present in a position to discuss. We are not yet in a position to separate the substratum, the living organism, from the essence, the actual specific ferment. There are other experiments known which make the search for such a separation appear still more unproductive. The question of the connection of fermentation phenomena—understanding in its widest sense the action of an organised element—with the physiology of plants (Sachs, Pfeffer), may be answered in a tolerably precise manner. We will confine ourselves to the carefully studied alcoholic fermentation as the prototype, but remark expressly, that the data given here

respecting that fermentation may be properly applied to ordinary putrefaction, or wherever organised ferments are concerned. Fermentation products are, according to this view, the expression of a progressive metamorphosis of organic matter (carbo-hydrates, proteids) by the oxygen of the air imprisoned in the living cells* of the particular ferment excitor. The products of this metamorphosis, by the aid of osmosis, get back from the cells into the surrounding medium. They are also, as Boussingault maintains, in a certain degree the secretion of the cells. This metamorphosis of the cell contents, or a part of them, as, for example, in saccharo mycetes, which produces alcohol and carbonic acid, is the consequence of one of the self-exhausting processes in the cells, which the vegetable physiologists call "their internal respiration" or "intra-molecular respiration" (Pfeffer). The proximate cause of this is probably the temperature, so that a minimum production of fermentation begins at 0°, reaches its maximum at 40°—50°, and stops altogether at 70°—75°. But fermentation or rather its products are not to be detected, so soon as the oxygen of the air has unrestricted entrance to the fermenting mixture. For all that, this intra-molecular respiration persists during unlimited introduction of oxygen. It does not attain to a concrete expression because its products are arrested by the free oxygen, and ultimately burnt to carbonic acid and water. These two processes, temporarily divided, decomposed into their two phases, indicate that the yeast in a solution of sugar, by respiring free oxygen without forming alcohol, uses just as much sugar as it would use in fermentation. On the other hand, the occurrence of alcohol and sugar in the above-related observation of Lechartier and Bellamy, is nothing more than the consequence of the self-exhausting "intra-molecular respiration" in the cells of the fruits and leaves, which we, if I may use

* Fermenting yeast cells placed in a solution of sugar in distilled water continue for a long time to form alcohol and carbonic acid.

the expression, surprise to a certain extent in its intermediate stage when we cut off its necessary oxygen. Under ordinary circumstances we do not observe this formation of alcohol, because it is oxidised further by the free oxygen of the air, and is decomposed into its ultimate products, carbonic acid and water. The followers of the doctrine of chemical ferments may regard this intra-molecular respiration as the consequence of a special chemical ferment contained in the cell, and accept, as M. Traube does for yeast, a special, as yet hypothetical and undemonstrated, alcoholic ferment.

Still the two following facts cannot be reconciled with this view:

First, it is known that not only yeast becomes useless after a time if it does not get fresh oxygen, but that all ferment-exciting hypho- and schizomycetes are only to a certain degree independent of free oxygen, and their growth and their accompanying fermentations are conditioned by it. But there are between the growth of the spores by exclusion of oxygen and the death of phanerogams only quantitative differences, such as exist between the winter sleep of a marmot and the normal tissue metamorphosis of an animal. This is not reconcilable with the properties of unorganised (chemical) ferments, which can carry on their fermentative action unimpaired without oxygen (Hüfner) and within very narrow limits. Secondly, in consequence of Lechartier and Bellamy's observation, we must admit the existence of such a ferment in every cell. Fermentation would be nothing more than "intra-molecular respiration," and we should find ourselves arguing in a circle to which there would be no end. Therefore all tissue metamorphoses, which find their limits with the death of the organism and are dependent upon its existence, as the tissue metamorphoses of the higher plants and animals are dependent upon their lives, and are not capable of being originated apart from the same through their elements, are not to be

described as fermentations. "Ferments" in this sense, then, are only the "chemical or unorganised ferments." There are other facts and theories which are not reconcilable with the above definition of all so-called "fermentations."

It will not have escaped your notice, on calling to mind the views that Pflüger has of late expressed on the subject of animal combustion, that this so-called "intra-molecular respiration" is nothing but the process which Pflüger has described as "dissociations-process" in animal cells, that is, a decomposition of a complex molecule into simple ones, or the intra-molecular striking off of small fragments from larger ones. Pflüger recognises in it the peculiar essence of all vital processes, the starting-point of the complicated phenomena which make up the life of the individual.

I am unable to do more than glance superficially at these far-reaching and important relations, and must leave you to decide, so far as you can, from the facts I have brought before you, in one or the other direction, either for the ubiquitous "chemical ferments," or for the exclusion of the "organised ferments" from fermentations proper.

For the present let us keep to the very convenient division into organised and unorganised ferments. All *purely physiological* fermentations in the animal body correspond to the unorganised, all *pathological* to the organised ferments. As the prototype of the latter, so far as our observation goes, we may name yeast (saccharomyces cerevisiæ and ellipsoideus), the lactic acid ferment (ferment lactique, Pasteur*), acetic acid ferment (mycoderma aceti), butyric acid ferment (baccillus subtilis, Cohn), and the urine or ammonia ferment of Van Tieghem (micrococcus ureæ, Cohn), which together with uric acid crystals and ammonium magnesium phosphate forms the white layer on the floors of urinals; finally, the ordinary putrefactive fer-

* The oidium lactis falsely confounded with this is, according to Reess, a mould, which also grows in sweet milk, and has nothing to do with the fermentation.

ments, bacteria and vibriones. The unorganised ferments are ptyalin in saliva, pepsin in gastric juice, pancreatin or trypsin in pancreatic juice, invertin in the intestinal juice, and a sugar-forming ferment present in fresh bile. These ferments formed in the animal bodies have been recently termed "enzymes." It was never doubted that the unorganised ferments are the products of organic bodies, which can prove their genealogy clearly and distinctly, and which at one point are united to the chain of organic life. It is quite otherwise for the organised ferments. The stringent proof that the putrefying or fermenting fluids do not contain organised elements within themselves, but introduce them from without, is extraordinarily difficult to produce, and has in the shape of the question of generatio equivoca or abiogenesis, the fundamental significance of which is obvious, occupied the learned world from Needham's time, 1745, to our own day. You know that it is principally being fought out over putrefactive ferments, vibrios and bacteria, but that it applies generally to all organised ferments. The decision of these questions is of the utmost importance to the pathology of digestion, and thereby justifies a short account of the same. The entire dispute between the panspermists and heterogenists has always turned upon the fact, that if one side brings forward experiments which prove that under proper regulations no spontaneous development of vibrios and bacteria takes place in a suitable nutritive fluid, the other side maintains that in consequence of these regulations the nutritive fluid has lost its nutritive qualities, and therefore a spontaneous development of ferment is impossible; and, on the other hand, if the others believe they have proved spontaneous development, their opponents maintain that either the originally present germs were not removed or made innocuous, or the entrance of the same during the experiment was not excluded. This is the constantly repeated train of ideas in the works of Schröder, Dusch, Schwann, Helmholtz, Wyman, Bastian, Huizinga,

Geschleidlen, and many others. Pasteur first, who in the year 1856 brought forward a series of pioneering observations on ferments and fermentation, "qui ont fait cette question presque la sienne" (Guillaud), succeeded by his numerous able researches in establishing, as it appears to us, the irrefragible proof of panspermism, the quintessence of which is included in the following points, which were proved by strict experiments:

1. There are at all times in the atmospheric air germs present which are necessary to the development of vibrios and bacteria, but the quantity varies with the locality. In pure land air and on the tops of mountains they are present, as Cohn, Burdon Sanderson and Rindfleisch ascertained, in smaller quantities than in the impure air of towns. 2. The nutritive fluids do not, by the manipulation which destroys the contained germs, lose the capacity to take up new germs, and to bear and nourish vibrios, when unheated air is admitted to them. 3. The germs contained in the air or the vibrios themselves are destroyed by the prolonged action of red heat, so that in suitable fluids they are no longer capable of development, whilst they stand temperatures of 120—130 C. without damage. 4. In nutritive fluids free from ferment, to which air is admitted, the same organic forms are found in 24—48 hours as in open fluids, but an alcoholic fermentation was never established, although the possibility of this on the part of the fluids is conceded.

These are the fundamental observations from which the following corollary may be drawn, which is of special interest for us practitioners of medicine. If arterial blood, under the necessary precautions, be introduced into a receptacle which was submitted to glowing hot air, and to this similarly glowing heated air be admitted, no putrefaction follows, an observation which demonstrates before our very eyes the untenability of the doctrine of a spontaneous putrescence of the blood, the putrid fever of the old writers, which played so

great a part in humoral pathology, and even now-a-days springs up here and there. The method of these experiments is so simple and ingenious, that I must explain it in one or two words. Imagine a T tube which is connected at one end with a red-hot tube from a furnace, through which air can come, and the other end with an air-pump, and the third with a somewhat short tube in which is a solid piece of glass. Each division may be shut off from the others by a stop-cock. In the other opening of the short tube there is hermetically fixed the finely drawn-out and sealed end of a retort, in which, before sealing, the nutritive fluid* was exposed to the necessary temperature for destroying the germs. It is now clear that, with the aid of the air-pump, first the space from the retort to the stop-cock, which goes towards the iron tube, may be made airless and then filled with glowing hot air, which by proper arrangement of the stop-cocks and use of the pump may be at pleasure removed and renewed, until we are sure that all unheated air has been driven out. If now the hard piece of glass in the wide tube be allowed to fall upon the point of the neck of the retort so as to break it, the nutritive fluid will be brought into contact with the heated air, and the result will be the absence of any putrefaction. The variations of this experiment require no further explanation. It appears to us that these beautiful experiments of Pasteur's decide once for all the doctrine of generatio equivoca, and with that the question of the spontaneous appearance of organised ferments. Wherever fermentative or putrefactive organisms are present, they are introduced from without, although their extraordinarily wide distribution and the consequent innumerable possibilities make a strict proof of their introduction not always possible. These observations also show that without the entrance of organised elements no putrefaction

* The so-called Pasteur's fluid contains: aq. distil. 100.0, sacch. crystall. 10.0, ammon. tart. 0.2—0.5, pot. phosph. or yeast ash 0.1.

occurs; and so you see I was justified, when previously quoting the observation of Hoppe-Seyler respecting the sealed hydrocele fluid and its putrefaction without vibrios, in desiring its confirmation. Therefore there is no proof that any fermentative process can occur without the concurrence of living cells, hypho- or schizomycetes.

The biological questions we have discussed are very intricate and still *sub judice*, but the accompanying chemical processes are clearly defined in many respects. We have already related a cardinal factor of fermentation, namely, that it occurs by taking up water. On the intimate nature and mode, how and in what part of the molecule it occurs, the following important table from Hoppe-Seyler indicates. But, above all, you will obtain from it an insight into the different fermentations, so far as they interest us, and with its help you will be able easily to discover your whereabouts in the future: we have already spoken (p. 9) of the other factors, so that I may avoid their repetition, and can pass on now to what is more strictly our subject.

Process of Fermentation.

1. Conversion of anhydrides into hydrates.

Ptyalin { Starch or glycogen to dextrine and grape sugar.
$2\ (C_6\ H_{10}\ O_5) + H_2\ O = C_6\ H_{10}\ O_5 + C_6\ H_{12}\ O_6$

Invertin { Cane sugar to levulose and grape sugar (dextrose).
$C_{12}\ H_{22}\ O_{11} + H_2\ O = C_6\ H_{12}\ O_6 + C_6\ H_{12}\ O_6$

Emulsin { Amygdalin to grape sugar, oil of bitter almonds.
$C_{20}\ H_{27}\ NO_{11} + 2\ (H_2\ O) = 2\ (C_6\ H_{12}\ O_6) + C_7\ H_6\ O +$
hydrocyanic acid.
H C N.

Pepsin
Pancreatin (Trypsin) { Albumen + n $(H_2\ O) =$

Pepton
Leucin
Tyrosin
Xanthin
Asparaginic acid

Pancreatic ferment, breaking up fats.	Tristearin to glycerine and stearic acid. $C_{57}H_{110}O_6+3(H_2O)=C_3H_8O_3+3(C_{18}H_{36}O_2)$
Urea decomposition by micrococcus ureæ.	Urea — Carbonate of ammonia. $CH_4\,N_2\,O+2\,H_2\,O = CO_3\,(NH_4)\,2$
Butyric acid fermentation by baccillus subtilis.	Lactic acid $2\,(C_3\,H_6\,O_3)+2\,(H_2\,O)=$ Butyric acid + carbonic acid and hydrogen. $C_4\,H_8\,O_2+2\,(CO_3\,H_2)+H_4$
Putrefactive processes the ferments of which have not yet been isolated.	Hippuric acid to glycocoll and benzoic acid. $C_9\,H_9\,NO_3+H_2\,O=C_2\,H_5\,NO_2+C_7\,H_6\,O_2$ Taurcholic acid to taurin and cholic acid. $C_{26}\,H_{45}\,NSO_7+H_2\,O=C_2\,H_7\,NSO_3+C_{24}\,H_{40}\,O_5$ Cellulose to carbonic acid and marsh gas. $n\,(C_6\,H_{10}\,O_5)+n\,(H_2\,O)=3n\,(CO_2)+3n\,(CH_4)$ Albumen + n $(H_2\,O)$ to Globulin, Peptone, &c. Leucin Tyrosin Xanthin Indol, Phenol, Scatol Fatty acids Carbonic acid Ammonia Sulphuretted hydrogen.

2. Conversion with passage of oxygen from hydrogen to carbonic acid atoms.

Alcoholic fermentation.

Yeast.	Grape sugar to alcohol and carbonic acid. $C_6\,H_{12}\,O_6+2\,(H_2\,O)=2\,(C_2\,H_6\,O)+2\,(CO_3\,H_2)$.

Lactic acid fermentation.

Ferment lactique (Pasteur). Bacterium lacticum (Cohn).	Milk sugar to grape sugar to lactic acid. $C_{12}\,H_{22}\,O_{11}+H_2\,O=2\,(C_6\,H_{12}\,O_6)=4\,(C_3\,H_6\,O_3)$.

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LECTURE III.

Gentlemen,—From the simple sac-like invagination of the asteridea, into which the "moving ocean" drives the food of the animal, up to the complicated gastro-intestinal system of the ruminants, with their three stomachs, the intestinal tract and its appendages fulfil the needs of each animal species in a wonderful manner. This is strikingly expressed, amongst other things, by the relation of its length to the length of the body. It is, on easily understood grounds, largest in the ruminants, as 15—20 : 1 (in the sheep 28 : 1); in the carnivora as 4 : 1, and midway between these stands man with 6 : 1. Swammerdam has shown that the tadpole, which lives on plants, has an intestinal canal about nine times the length of its body, whilst in the frog, which lives on animal food, the relative length falls to 2 : 1.

That the digestive tube in the higher animals also is merely an invagination of the surface of the body, is suggested by the prolongation of the epithelium of the epidermis into its oral and aboral openings; but it stops there, and there is another kind of epithelial layer where the special work of digestion begins. The above-mentioned appendages, which prepare the digestive juices (so far one can regard the stomach as a sac-like appendage of the intestine), are not so uniformly distributed through the animal series. They are present

equally in all vertebrata, with the exception of the pancreas, which is absent in many fishes; and this fact should have impressed on our predecessors that a principal and fundamental distinction between herbivora and carnivora, corresponding to the nature of the digestible matter, does not exist. On the other hand, stomach, liver, pancreas, &c., are absent, sometimes singly, sometimes entirely, in the invertebrata, conditions which cannot be gone into now. We turn chiefly—as we must set aside the mechanical part of digestion and what belongs to it, the ingestion of food and drink, mastication, the teeth, deglutition, the mechanism of defecation, &c., as well as the coarse anatomical description of the organs—without further remark, to direct our attention to the structures whose secretions occasion, at least in the main part, the chemical and physiological processes in the digestive tract.

Of the four gland groups, the united secretions of which formed *the mixed saliva*, we will first take the submaxillary glands, not only because the classical investigations of C. Ludwig and Cl. Bernard discovered in them an apparently inexhaustible field of fruitful physiological investigations, but also because in them the processes of glandular activity, κατ ἐξοχην, are most instructively studied, and the fundamental data for the theories of the secretion of glandular organs have been derived from them. Do not be surprised, therefore, if we occupy an apparently disproportionate amount of our time on the study of the submaxillary glands.

The minute structure of these glands, which belong, as do all the salivary glands, to the acinous type, has been studied, especially in the dog, rabbit, cat, calf and sheep, and its anatomy known completely. A number, mostly 5—10, of epithelial cells group themselves round the commencement of the excretory duct, which lies in the middle, from which, as I have proved by injection, fine processes ramify between the cells out to their common envelope, the membrana propria. The latter is a structureless membrane

stretched between peculiar connective tissue-like cells with rib-like processes, so-called basket cells (Henle, Boll), and cuts the cells off from one another and so shapes the alveolus. Each alveolus is attached to the duct like a raspberry to its stalk; the latter is covered with a special very finely striated-looking epithelium (Pflüger). Under ordinary circumstances, as for instance when the animal employed has not lost an unusual amount of saliva before the gland was removed, the special gland-cells contain two zones, best seen in alcohol preparations, less distinctly in fresh sections—an outer granular layer, containing flattened nuclei, protoplasmic and lying against the membrana propria, and a glass-like mucous inner zone, turned towards the commencement of the excretory duct, which in extent surpasses the first. The entire outer zone has its nuclei easily stained with colouring agents (carmine, hæmatoxylin, &c.); the inner remains unstained. In many alveoli, especially frequent in the gland of the sheep, much more rarely in the dog, some of the cells are smaller than the others and contain only protoplasm. They lie close under the membrana propria, and bend the other cells into a sickle-shape, so that Gianuzzi has described these complexes of cells as "half-moons" (halbmöndchen). Heidenhain believes that they represent an early stage of the others. If the gland is irritated, either reflexly from the mucous membrane of the mouth or directly from the nerves, so as to continue secreting for an hour or more, we find, as Heidenhain discovered, an altered condition on similar preparation of the gland from that which filled it in the first, and especially in alcohol hardened preparations of an "unstimulated" example. The alveoli are all smaller, the interalveolar connective tissue is more distinct. Nothing is to be seen of the hyaline inner zone of cells; they are filled with brightly-stained protoplasm; the nucleus is pushed up to the middle, is large and round; the distinction between the "half-moons" and the rest of the alveolus has disappeared. Whilst a stained section of

the unstimulated gland looks clear on account of the preponderance of the unstained mucus, the sections of the stimulated gland present a universal, vivid colouration from the staining agent employed, as you may perceive in these two preparations stained with hæmatoxylin ; in short, there is such an enormous difference between the stimulated and unstimulated gland, that it never could be guessed that both were derived from the same organ. The passage from one to the other condition may be observed in all the intermediate stages of the gradual disappearance of the mucus and the recoil of the protoplasm. In the fresh state, Langley found the alveoli of the unstimulated gland formed of a mass looking like ground glass, which changes during secretion into a granular appearance, which disappears first on continued stimulation from the peripheral parts of the cells. In this way, a clear outer zone and a more granular centre are formed. This is the opposite of what occurs in the hardened gland, which is evidently altered by the hardening process. According to Heidenhain, the original cells are completely disorganised by their protoplasm becoming mucus, and in the "stimulated" gland we have before us only the young after-growth of the "half-moons" as a consequence of a trophic "nerve-action." I formerly sought to prove that the cells persist and only lose their mucus, and that one can obtain the appearance of a stimulated gland without physiological stimulation by withdrawing the mucus from the cells in another way. A "trophic nerve-action" in the sense of cell-formation I believed must be denied. According to Heidenhain's recent observations, which I have to describe to you directly, it is no longer doubtful that "trophic nerves" run into the glands, if we mean nerves which by the action alter the cell contents chemically and histologically.

I should consider it very dogmatical to contradict the conclusions of this observer from my former standpoint. Matters are quite changed from what they were at the time

when I understood by trophic nerve-action the growth from the half-moons. But the destruction of individual cells and their repair by an immediate new formation during the relatively short period of stimulation, as Heidenhain holds for the salivary glands, appears to me still doubtful. I have had the opportunity of examining the salivary glands of a newly-born dog, which, as you can perceive for yourselves and as Heidenhain has stated, have entirely the character of stimulated glands. This animal had not formed any saliva yet which could fill the cells and displace their protoplasm. We shall return to this point once more in speaking of the conditions in the pancreas.

The secretion of the glands is excited through nerve filaments which run in part in the chorda tympani, in part in the sympathetic, and influence the gland parenchyma, not continuously but periodically. Their terminal branches have been traced by Pflüger up to the individual gland cells; he considers the salivary cell directly "as a swelling on a medullated nerve," and "the gland cells as budding outgrowths of the nerves," so that he in this fashion places the most intimate continuity between the nerve and cell. This statement of Pflüger's at present remains unconfirmed. At all events, the gland obeys the nerve as a good horse his rider, and nothing is so surprising as to see how drop after drop flows from the canula fastened in the excretory duct, when one of the above nerves is excited. By means of electricity the gland may be made to secrete for hours, even for a whole day, if care is taken by the use of a weak current and short pauses, not to exhaust the nerve and gland-parenchyma too early. It is known that at the same time the temperature of the gland rises as much as one and a half degree of the Centigrade scale, that the blood stream is hastened, that the venous blood escapes of an arterial colour; the pressure in the salivary duct when connected with a manometer rises higher than the pressure in the gland artery, and a pure, aqueous, slightly fibrin-forming

secretion is poured out. Only the first few drops of the secretion are made turbid by epithelium and other elements of the tissues—products of the irritation of the duct by the canula—as well as by crystals of oxalate of lime which are separated during the stagnation in the duct. Pure saliva is free from morphological elements. All this applies only to the secretion obtained by exciting the chorda, the "chorda saliva." The "sympathetic saliva" is thicker, jelly-like, much richer in mucus, is secreted in much smaller quantity, and instead of widening there occurs a narrowing of the vessels and slowing of the blood-stream. If acids or alkalis are injected into the duct (Gianuzzi), or the animal is poisoned by injecting atropin into the circulation (Heidenhain), and the chorda be then stimulated, no secretion follows, but the vessels become dilated and red blood flows out of the divided veins. (For this purpose a large dog requires 8—10 milligrammes of sulphate of atropia). There must, therefore, be two sets of fibres in the chorda, one quickening the circulation, the other increasing secretion, or these latter fibres, or their peripheral organs, the cells, may be paralysed by the said injections. If, whilst the gland is under the influence of these poisons, the sympathetic be stimulated, the ordinary sympathetic secretion is obtained. The cells are therefore capable of acting, and consequently the chorda nerves must be paralysed, and thence it follows that the chorda and sympathetic fibres run separately up to their terminations, and have different points of connection with the gland cells.

The known antagonism between atropin and eserin suggests the experiment to obviate the action of atropin poisoning by injecting a requisite dose of extract of physostigma, and this is in fact possible. If salivation is induced in an animal by injection of pilocarpin, and then atropin be given, the flow of saliva ceases. But after the injection of the requisite dose of eserin, the saliva begins again to flow from the canula spontaneously, or after a small dose of

pilocarpin. These beautiful data are a series of observations of Heidenhain's, but they are not only of importance for the salivary glands, but bear, as it is scarcely necessary to insist upon, a universal significance. It is being shown daily that apparently uniform nerve fibres included in a common sheath possess not a uniform, but a very different action on the peripheral organs. I refer to the sciatic, and by the above observations Heidenhain has given us another exceptionally clear instance of this condition. I shall be able to show you the experiment, which is not difficult to perform, and which I have already repeated many times. At the same time you can observe the salivating property of hydrochlorate of pilocarpin, which we can employ instead of the electric current. The action of pilocarpin is paralysed by atropin, and this again by eserin. Langley described a method by which the chorda tympani nerve can be paralysed by atropin and restored by pilocarpin for an almost unlimited number of times, by injecting atropin into the blood and warm pilocarpin into the duct of the gland.

The constituents of the normal chorda saliva are approximately as follow: the normal numbers cannot be given here or elsewhere.

Water	996.04		
Solid residue	3.96—of which		
		Inorganic	2.45
		Organic	1.51

The organic constituents are: Mucin, which is precipitated as a whitish or fibrinous cloud when I let fall a drop of saliva into a test-tube of water acidulated with acetic acid; traces of albumen, proved by a slight cloudiness on boiling, the xanthoprotein reaction (boiled with nitric acid forms a beautiful orange red colour by adding ammonia), and the test with ferrocyanide of potassium and acetic acid (white precipitate). The submaxillary saliva also contains a ferment, called ptyalin, which converts sugar strongly. Grützner disputes

its existence. I have myself repeatedly observed that pure submaxillary secretion obtained from a fistulous opening acts like diastase after some time (1 hour). But the rapidity of its action is far less than that of the parotid saliva, the mixed saliva of the mouth, or pancreatic juice. The extract of the glands of newly-born children, according to Zweifel, has no diastatic action; as well as, as may be stated in anticipation here, the parotid extract. The organic constituents are chloride of sodium, chloride of potassium, carbonate and phosphate of lime, phosphate of magnesia and phosphate of soda. The sympathetic saliva is richer in mucin, poorer in water, and has, therefore, a much higher percentage of organic constituents than the chorda saliva. The solid constituents of the saliva diminish with the duration of the stimulation—the organic more than the inorganic (Ludwig)—and rise with the strength of the nerve irritation. Lastly, on the condition that the water and inorganic salts increase *pari passu* with the strength of the stimulus, the organic constituents increase at first more rapidly than the salts, but after the lapse of a certain time they decrease as the gland gets exhausted. If the stimulus is diminished, the quantity of salts in the secretion begins to be diminished, and they decrease more rapidly than the organic matter, so that their total excretion becomes less than the latter; in one case the organic constituents are surpassed by the inorganic, and in the other case they are more persistent; both quantities are to a certain degree independent of one another, or, in other words, *the quantity of organic matter is not only conditioned by the strength and the duration of the stimulus, but also by the state of the gland* (Heidenhain).

These are very complicated conditions, which we want to make as clear as possible, because, as we shall see directly, they afford a very significant point of departure for the theory of secretion.

Finally, there are gases in the saliva, free carbonic acid and nitrogen. If the duct be tied, considerable œdema of

the gland occurs. The so-called "paralytic" saliva is the secretion of saliva which sometimes occurs after section of the nerve, and often continues for days, and which, discovered by Bernard, has defied all explanation hitherto.

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LECTURE IV.

Gentlemen,—The remarkable discoveries to which the thorough investigation of the submaxillary glands has led, demand a somewhat deeper acquaintance with an organ so specially interesting for many reasons. The description of the other salivary glands may, nay must, be short, because we know but little about them.

The parotid is absent in birds, because it is the masticatory gland κατ' ε'ξοχην, and grows in the animal series in proportion to the development of the masticatory apparatus. Its *histological* conditions are very similar to those of the submaxillary. But there is no mucus in its cells; they are uniformly filled with protoplasm; the mesially placed nucleus stains strongly with carmine, whilst the rest of the cell is only slightly stained. Here, as before, a change in the microscopical structure occurs on stimulating the nerve, with this difference, that it is brought about, not by irritating the cerebral nerve, but the sympathetic. The cells shrink, become very cloudy; their protoplasm is better stained by carmine; the round, many-nucleolated nuclei become very distinct. This apparent difference of nerve action will in truth prove to be an analogy, so soon as we have shown more completely the influence of the nerve on the gland. The special glandular nerve is the auriculo-temporalis, which unites with the small superficial

petrosal nerve at the otic ganglion; the latter is connected with the glossopharyngeal through the ramus tympanicus (N. Jacobsonii), and so conveys reflexes from the cavity of the mouth to the gland. Heidenhain, whom we have again to thank for our exact knowledge of details, stimulated the nerve from the tympanum. Moreover, the gland may be stimulated from the sympathetic. In this case also the circulatory conditions are, as in the submaxillary, dilatation of vessels and quickening of the blood-stream on stimulating the cerebral nerve; with narrowing of the vessels and slowing of the blood-stream on stimulating the sympathetic. Here also the pressure (118 m.m. mercury) of the secretion in the duct may be made by continuous stimulation much higher than the blood pressure. Moreover, there is in this gland a notable relation between the irritation of the sympathetic and cerebral nerves. The irritation of Jacobson's nerve only, for instance, gives an aqueous secretion free from mucus, which contains a little albumen, paraglobulin, a diastatic ferment and the usual salts. The total of solid constituents in this secretion is small, and of these the organic are less than the inorganic. The irritation of the sympathetic is followed generally by no secretion. But if the nerve of Jacobson and the sympathetic are stimulated at the same time by two electrodes, the secretion not only becomes richer in solid constituents, but the relations between organic and inorganic are so upset that the organic preponderates. For instance:

	Solids.	Salts.	Organ. matter.
N. Jacobs. alone	=0.56	0.31	0.24
N. Jacobs. + sympathet.	=2.42	0.36	2.06

This suggests that the basis of this relation may be sought for in the contracting effect of the sympathetic on the vessels. But apart from the fact that the quantity of salts in both cases is approximately equal, that during simultaneous stimulus of both nerves being rather the greater, this idea is directly disproved by the observation that tying the

carotid has no influence on the experiment, although this would produce much greater interference with the circulation than stimulation of the sympathetic. We must also admit that the cerebral nerve presides mainly over the excretion of water and salts, the sympathetic governing the passage of organic matter into the secretion by the formation of soluble substances in the cells. When we learn, too, that similar changes in the contents of the secretion, in salts and organic constituents, follow the duration and intensity of the secretion as in the submaxillary, and that the contents of the secretion in organic matter stand in no direct relation to the quantity of water which the gland secretes, we cannot avoid the conclusion that the sympathetic nerve exerts a specific "trophic" influence on the gland cells. The nerve of Jacobson governs mainly the separation of water, while the sympathetic presides over the formation of the specific elements of the secretion. For the same reasons we were obliged to admit the existence of two kinds of nerve fibres in the chorda, water-secreting and mucus-secreting nerves, only they ran together in one nerve sheath, while they go separately to the parotid. This explains why the change in microscopic structure, which consists chiefly in the changes in the organic gland substance, in one case is brought about by stimulus of the sympathetic, in the other of the chorda. If I first irritate the cervical sympathetic of this rabbit with a canula placed in Stenson's duct according to Heidenhain's method, until I have obtained about 1 cm. of secretion, and then invoke the cerebral nerves by injecting pilocarpine into the veins, and collect the same quantity of secretion, you see that the sympathetic secretion becomes a jelly-like coagulum by heating, while the cerebral secretion becomes only feebly turbid, although both looked equally clear before.* A proof of the richness of the sympathetic secretion in albumen.

* This experiment was performed on the 20th October, 1878 (after Heidenhain).

In man, a fine silver canula may be easily introduced, as I show you here, into Stenson's duct, and a copious secretion takes place, chiefly by reflex action. This secretion is alkaline, but, according to Astaschawsky and Mossler, with moderate secretion, or when fasting it is feebly acid, free from mucin and has a diastatic action. In diabetics, though not invariably, it contains sugar, which is sometimes so abundant that its presence can be proved by fermentation, reduction and polarisation.

We know little about the *sublingual gland*, which is formed on a very similar type to the submaxillary. It furnishes a secretion similar to but more viscid than the last, which may contain as much as 2.7 per cent. of solids, and is controlled by nerves which run in the trunks of the chorda and sympathetic. Beyer, working under Heidenhain's direction, found that the alveoli alter their appearance during secretion, in the same manner as in the submaxillary gland.

The secretion of the *buccal and labial glands*, likewise acinous glands, may be obtained pure only after tying all the other ducts. But the significance of such an experiment does not repay the trouble involved, as the difference between the mixed oral saliva and the secretions of the particular glands already described, shows that the glandulæ buccales et labiales separate a mucous secretion very like that of the other glands. The product of all the secretions poured out into the oral cavity forms the mixed or oral saliva, the composition of which has been anticipated in what has been said already, so that I need only mention that its sp. gr. is from 1004—1009, and emphasise the fact that the much talked-of sulpho-cyanide of potassium obviously arises as a decomposition product in the cavity of the mouth—perhaps, according to Pettenkofer, being derived from urea and sulphate of potash. The reaction is ordinarily alkaline, but in many pathological conditions, as in fever and diabetes, it is acid. This depends upon an acid fermentation of matters present in the mouth

at the same time, or perhaps upon the above-mentioned property of the parotid saliva to become acid under certain conditions. Incidentally I may mention the morphological elements of the mixed saliva cells, namely, the salivary corpuscles distinguished by their active molecular movements, and abraded epithelial scales. But for us the existence of the diastatic ferment, *ptyalin*, is of greater significance. We have not succeeded in obtaining pure ptyalin. As is so frequently the case in fermentation processes, we conclude from the known action of the secretion the presence of a ferment to which we have given a name, but have not yet obtained in all its purity. It is Cohnheim's merit to have first obtained a diastatic and approximately pure preparation from human saliva. A most simply performed experiment teaches how rapidly and energetically mixed saliva converts starch into maltose and sugar. Sugar is formed from starch, probably by means of the intermediate products achroodextrine and erythrodextrine, two bodies standing very near to starch (see the table in Lecture II.)—a process which, according to Paschutin, takes place most quickly in boiled starch paste at 38°—41°C. Mixed saliva changes starch into sugar not only in alkaline and neutral, but also in acid solutions. The food passes through the mouth so quickly, that there can be scarcely any question of the occurrence there of an extensive chemical action, and besides the greater part of the saliva is swallowed; so with respect to the special evolution of its diastatic function, it signifies very much how the relations shape themselves in the stomach, to which we shall return in the proper place. A second very important property of the saliva is to lubricate the morsels of food. The following observation of Cl. Bernard's, demonstrating this very clearly, is little known and is worth relating. The œsophagus of a horse was opened, and boli of moist oats were given by the mouth, which every 1—1½ seconds came out of the opening, so that in nine minutes 500 grms. had passed. But when the

parotid ducts were cut, the parotid secretion, and therewith the chief part of the saliva, being made to flow externally, the boli appeared only every 1—2½ minutes—in 25 minutes only 360 grms., which gives a difference per minute of 41.1 grms. At the same time it was noticed that during drinking, the secretion of the parotid (and probably also of the other glands) ceased entirely.

The quantity of saliva for the 24 hours is estimated by Bidder and Schmidt to be in man 1500 grms. Tuczek estimated by a special method how much saliva was taken up by a well masticated and afterwards expectorated morsel of food, and found, as was to be expected *a priori*, that the poorer the food was in water the more saliva was secreted. In this way there were secreted daily, with black bread 545 grms., with white bread 698, with mixed diet 476, with bread and potatoes 659, with highly albuminous diet 773 grms. of saliva. Both sides of the oral cavity do not share equally in this work of secretion. Pflüger found that a third more was secreted on the masticating side than on the other.

What influence the suppression of the entire salivary secretion has on the general health cannot be stated, because such cases, with the exception of the local and transient diminution of saliva in fever, in many cases of poisoning, &c., are not known. Zweifel has found the diastatic action of the parotid unchanged by the diseases of children. The loss of saliva through fistulous openings does not appear to have any particular consequences, although an English author, Wright, who collected for purposes of observation 250 grms. of his saliva in one week, lost 11 pounds weight (?).

On the other hand, the pathological increase in the secretion of saliva does not permit its consequences to be distinguished from those of the original affection; but if we may judge from the cases of ptyalism in hysteria, paralysis, &c., it may continue for a long time without injury to the health. Finally, as a curiosity, may be mentioned the cases of

intermittent sialorrhœa, which, according to Rayer, are described as recurring about every 30—50 days. From the phosphate and carbonate of lime in the saliva, which become partly decomposed and combined with organic matter (mucin, albumen, fungi), arises the formation of salivary calculus and the plugging of a salivary duct, with its consequences.

I cannot leave the subject of the salivary glands without referring to a view which Heidenhain has expressed with reference to an old view of Hering's on the process of secretion. When you remember the remarkable condition, that the pressure in the salivary duct is higher than the blood pressure; when you think of the fact that the poisoned cells of the submaxillary gland stimulated from the chorda, in spite of the quickened circulation, do not secrete while there is neither œdema of the gland nor increased flow of lymph, you will agree that the blood pressure cannot explain the process of secretion, and that the immediate cause must lie in the cells themselves, and not in the stimulating influence of the blood. We may fully admit that the circulation is only concerned so far as that it delivers the raw material, and meets an increased demand by an increased rapidity of the current. Hering held secretion in the salivary glands to be a process similar to the osmotic processes in plants, having its origin in the capacity of mucin for taking up water. He thus explained the fact that the salivary pressure is higher than the blood pressure, because it is known that extraordinarily high hydrostatic pressures are produced by osmotic actions. But this is refuted, amongst other things, by the circumstance that, as we have seen, in the parotid secretion, which is free from mucin, a similar high pressure occurs. One must ascribe this capacity of imbibition not only to the mucin, but also to the entire glandular protoplasm, which absorbs water out of the lymph vessels and blood in proportion to its hypothetical imbibing capacity, so that once for all the cell contents stand under a higher pressure than the blood. But these to a certain extent *compressed*

cell contents cannot flow out towards the duct before the stimulus of the glandular nerves indicates that the ordinary opposing forces are removed. Whether one should attribute this, with Heidenhain, to a molecular arrangement, or imagine a thermal influence which only concerns a part of the cell, and in this way permits a definitely directed osmotic nerve current, remains uncertain. In short, this explanation concerns only the water and salts. The organic matter, we have seen, is in a measure independent of the quantity of water secreted, and its quantity increases with the stimulus. Here comes in a peculiar function of the cell contents in the production of the specific elements of the secretion. Perhaps the following factor finds its place here, in addition to the so-called trophic nerve stimulus: Kühne and Lea have proved directly, in the case of the pancreas, that all parts of a secreting gland are not functionally active at the same time. Pathological facts, for example in the kidneys, show that all parts of a gland are not at all times equally active in secreting. If one part of the gland cells is active longer than the other, and consequently is in another stage of its work, perhaps it becomes early very exhausted, and thus differences can arise in the combined secretion during the different phases of the stimulus, which would explain Heidenhain's facts.

Similar remarks of a general nature upon the process of glandular functions, which we have brought forward with reference to the salivary glands, are applicable to the other glandular organs—for example, the gastric glands, the pancreas, Brunner's glands, &c. They gain, therefore, a general significance for the comprehension of the mysterious and wonderful secreting processes, so that equipped with these views we need not return to this question.

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LECTURE V.

Gentlemen,—Formerly we distinguished two forms of gastric glands, both tube-shaped, of which one occupies the fundus, and is lined with rounded nucleated cells, the so-called rennet glands (Frerichs); the other is situated in the pyloric portion, and is lined with a more cylindrical epithelium, the mucus glands. The former produce the well-known gastric juice, the rennet; the latter, mucus. In addition, some observers have found acinous glands (Donders, Frey). Meanwhile this simple explanation has undergone an important extension by the simultaneous publications of Rollet and Heidenhain. The structure of the gastric mucous membrane, as one may easily ascertain, is the following: The surface of mucous membrane lining the stomach is covered with a deep cylindrical epithelium, which passes into the openings of the gland tubules. In these, which have, like the salivary glands, a membrana propria strewn with stellate connective tissue cells, we can distinguish an upper, smaller part, the gland neck, and a lower, somewhat wider part, the fundus of the gland. In the neck the cells are placed in a single row on the membrana propria; in the fundus they are numerous and fill it out like stones in a bag. The cells are pushed together in the middle of the tube, and leave no distinct lumen to be recognised, but it is doubtless

present and is sometimes easily seen. In stained alcohol preparations one sees—particularly well in the dog and pig, indistinctly, after one has learnt their disposition in those animals, in man—in a longitudinal section of the glands of the fundus, that the "neck cells" for the most part are brightly stained, large, and have distinctly outlined nuclei, and in many places push out the membrana propria. In the gland fundus, on the other hand, we find smaller cells with distinctly coloured nuclei and granular unstained protoplasm, which are here and there replaced by a cell of the first-named sort, but which still preponderate in quantity and form the principal elements. Sections which have divided the gland neck vertically to the long axis of the tubule show a crown of regular, rigid, large, darkly-tinged cells, whilst sections of the fundus show an irregularly grouped quantity of uncoloured smaller cells, which are only here and there varied by a large, coloured, roundly-projecting cell placed on the membrana propria. The former are visible distinctly, the latter indistinctly; the former are few in number, the latter are relatively crowded and form the principal elements. Rollet distinguishes them as delomorphic and adelomorphic; Heidenhain, as pavement (Beleg) and fundamental (Haupt) cells. Between the tubules rises a sometimes greatly developed support of connective tissue, which exhibits a retiform structure in brushed-out sections. With it are organic muscular fibres, while the vessels of the sub-mucous trunks pass between the tubuli and form a narrow capillary network around the orifices of the glands. In the submucous tissue impinging on the fundus of the gland, I have described in man typical acinous glands without any recognisable excretory duct. Ebstein has undertaken a thorough investigation of the rennet and mucous glands of the pyloric region with reference to the above-mentioned description, and found that the pyloric glands have almost no pavement cells, but an epithelium, very similar to the fundamental cells of the

fundus glands, which behave themselves during digestion in a manner analogous to that which we shall immediately describe in the fundus glands.

If we trace the influence which the process of digestion and the function of the glands exercise on their structure, we find this at its acme, somewhere about the fourth hour after the ingestion of food; the tubes, as Frerichs already described, being swollen out, the fundamental cells very cloudy, swollen and (in stained preparations) coloured, the pavement cells still larger and more prominent than ever. These striking changes in the cells recede in the last hours of digestion, in which the distended tubes shrink, but the strong colouring of the fundamental cells remains a longer time, until it gives way to the normal condition. We see that, first, at the height of the digestive activity of the stomach, obviously more goes into than comes out of the cells, or they could not swell; and, secondly, their contents must be distinguished from those of the fasting state, or they could not exercise such a much greater absorbing power on the colouring matter of the staining agent. What the nature of this change may be, which in all probability represents the first stage of the special secretion, our pioneer (Heidenhain) has left unsettled. At a certain period of digestion, the pavement and fundamental cells must look very much alike; and I place before you preparations from the dog in full digestion, in which I can find no difference between the two kinds of cells, whilst the distinctions between the two kinds in the preparations from the fasting dog are very noticeable.

The influence of the nervous system on the stomach was till recently unknown, except that the innervation must run in the trunks of the sympathetic and vagus. We know now very little more, except that by peripheral irritation of the vagus we can give rise to irregular contractions of the stomach; the same results follow reflexes from the central

nervous system, in particular from the medulla oblongata, whether the reflex excitement be central or whether it be of peripheral origin, also in pathological instances, in the one case of injuries and diseases of the brain and spinal cord, in the other of irritation of the mucous or serous membranes, the sense organs (taste, hearing), dreams, &c. But the reflex action then asserts itself in a reverse movement, vomiting, which plainly, according to the well-known observations of Magendie, is much less dependent on the stomach than on the abdominal muscles. If we poison an animal with curare, which leaves the gastric nerves intact, it vomits no longer, because the abdominal muscles are paralysed. All more intimate knowledge of the glandular innervation is wanting. The statements of Cl. Bernard and Frerichs, that section of the vagi is followed by interference with the secreting functions, have been long ago contradicted, and we stand face to face with the bare fact that mechanical irritation of the gastric mucous membrane, whether by ingesta or otherwise, gives rise to hyperæmic reddening with copious secretion; whilst fasting stomachs, as I maintain with Hoppe-Seyler, contain no secretion, but only a little mucus. A contribution to the comprehension of the movements of the stomach has been recently made by Goltz. If we expose in a special manner the stomach and œsophagus of two vertically-hanging curarised frogs, so that they can be well observed, and drop a dilute watery solution of salt into both their mouths, after having previously destroyed the brain and spinal cord of one, the following occurs: The stomach and œsophagus of the unbrained frog are widely distended, full of fluid, quite motionless, only traversed by a to-and-fro peristaltic wave, and look like a blown-up pig's bladder. The œsophagus and stomach of the frog deprived of its brain are empty, and beaded in many places by sharp muscular contractions, which run peristaltically from above downwards. The same occurs when the

vagi are cut, whilst electrical stimulation of these nerves only causes slight contraction. This experiment, which may be extended by exciting reflex movements, is easily performed, and, as you see, is of striking significance. In fact, one can conceive no greater contrast than the stomachs of the two animals, especially as it increases with time; for the parts concerned in the frog deprived of its brain dry in the air quicker than the other. Goltz concludes from this that an independently acting system of ganglion cells (analogous to the plexus myentericus) is present in the stomach, the irritation of which gives rise to local contractions and peristaltic movements, but which is in connection through the vagi with the medulla oblongata, which exercises a controlling effect on the functions of these ganglia ;—an explanation which is quite familiar to us from the reflex controlling centres for the extremities in the spinal cord. If by destruction of the medulla or section of the vagi the controlling influence is wanting, a very strong action of the centres in the stomach follows stimuli which not only escape the observer, but are without effect on the normal stomach, just as we observe an increased reflex excitability in certain diseases of the spinal cord—for example, sclerosis, hemorrhage, &c. The theory unites proved and unproved views; moreover, the experiment succeeds invariably and without difficulty, the only drawback being that, so far, it has only been performed on frogs, and that the postulated ganglionic system has not yet been seen.

Pure, unmixed *gastric juice* was first known when Bidder and Schmidt produced gastric fistulæ in animals, and at the same time tied all the ducts of the salivary glands to prevent swallowing of saliva. Such gastric juice has the following composition :

	Gastric juice of Dog free from saliva. Mean of 10 analyses.	Gastric juice of Man containing saliva.	Blood serum of Man.
Water	973.06	994.6	903.0
Solids	26.94	5.4	97.1
Containing:			
Pepton and pepsin	17.19	3.02	Organ. mat. 88.5
Free hydrochloric acid	3.05	0.22	Inorganic 8.6
Alkaline chlorides	4.26	2.0	7.2
Ammonium chloride	0.47		
Containing chlorine	**5.06**		**3.6**
Phosphates: Lime	1.73		
Phosphates: Magnesia	0.23	0.15	0.5
Phosphates: Iron	0.08		

Here you have an analysis of human gastric juice as obtained from a gastric fistula, and the comparison with an analysis made by Lehmann of human serum. The large proportion of chlorine in the gastric juice as compared with blood serum will strike you, whilst, conversely, although it is certainly not distinctly brought out by the analyses, there is about one-half less alkali in the gastric juice than in blood.

The reaction of the gastric juice is always very acid. The mucous membrane of a recently killed animal possesses an acid reaction wherever it comes in contact with the gastric juice. There is little interest in following historically the discussion of the question as to which acids give rise to this reaction. Bidder and Schmidt have proved by an unimpeachable method that it is free hydrochloric acid. They estimated the entire chlorine and the entire bases, reckoning these all as chlorides, in a measured quantity of gastric juice, and found more chlorine than would be necessary to convert the bases into chlorides. This overplus of chlorine can exist only as hydrochloric acid, free or in an organic combination. But the excess of chlorine corresponds to the

equivalent of an alkali (Barium), which must be added to the same quantity of gastric juice as was used in the experiment up to neutralisation; so it follows that, first, free hydrochloric acid is present; and, second, other acids, if there be any, are present in only very slight traces. This investigation has finally decided the dispute concerning the nature of the gastric acid, which had attained such dimensions that no fewer than twelve authors have pleaded for lactic acid, fourteen for hydrochloric acid, and two for phosphoric acid. Now, as we know there is only one mineral acid in the gastric juice and that it is hydrochloric acid, we may decide the second question, whether it is present alone or in company with other organic acids, by the aid of another easily-performed reaction. Reoch's reagent serves chiefly to prove that hydrochloric acid is present in acid gastric juice. Equal parts of half per cent. solutions of sulpho-cyanide of ammonium and acetate of soda are poured together; 1 cm. of this pale yellow solution is coloured a brown or brownish red by treatment with 0.5—1 cm. of very dilute hydrochloric acid (Szabo gives to 1 per mille; I find the first distinct reaction at 2.5 per mille); whilst organic acids, such as lactic and acetic acids, give rise to the same reaction when more concentrated (not below 15—20 per cent.), but by their presence in feeble concentration they do not interfere with the hydrochloric acid reaction. Similar colour reactions are given by some aniline dyes in sufficiently dilute solutions—for instance, methyl-violet (known in histology for demonstrating the amyloid reaction), red fuchsin, and yellow tropæolin. The first becomes blue, the second yellow, the third red. Of all these, methyl-violet is the most delicate, as, according to my experience, the hydrochloric acid need not exceed 0.15 per cent. But if we wish to test simultaneously for organic and inorganic acids in the stomach—for gastric juice may, under certain conditions, be very acid and yet contain only small quantities of hydrochloric acid, together with much lactic acid, acetic acid,

butyric acid, &c.—we may employ the Richet-Berthelot method, which I will explain in principle, because it may be employed for pathological investigations, and Richet has by its aid re-investigated the question of the nature of the normal gastric juice, and solved the problem in harmony with Schmidt's conclusion. If you shake a simple acid solution with ether, the latter takes up a constant quantity of different acids, and the acidity of the decanted ethereal solution stands in a definite and constant relation to the acidity of the acid solution after shaking. The acidity is estimated by means of the quantity of lime water of known strength which is required to neutralise the fluid in question. This relation, called by Berthelot the co-efficient of partage, is very high for mineral acids—over 500—for organic acids lower, because it takes up mineral acids only in traces, but organic acids in greater amounts, and naturally, independent of the quantity, but in some degree dependent upon the concentration and temperature of the fluid investigated. The co-efficient of partage of, for example, benzoic acid is 1.8; that is, an unknown acid solution which after shaking with ether has an acidity = 1, whilst that of the ether = 0.55, must be a benzoic acid solution. In this manner we can define the nature of unknown acids, and feel sure there is only one acid present, if the co-efficient of partage after two or more shakings remains the same. But if we have to do with a mixture of two or more acids—for instance, one organic and one inorganic—they may be separated by one passing into the ether more easily, the other less so. By repeated treatment of the watery solution with ether (for the organic acid which is readily taken up by ether), and the original ethereal extract with water (for the inorganic acid), and estimation of the co-efficient of partage in each case, which increases or decreases until both acids are quite separated from one another, we finally obtain the constant co-efficient of partage for each of the acids present, and can tell whether an unknown acid solu-

tion contains organic or inorganic acids or both by this method, which is much more quickly performed than described. Richet was able to prove that there is *only one* mineral acid present in fresh gastric juice, but, as he concludes from further estimations, not existing free, but in loose combination with an organic substance, leucin, as chloride of leucin. Richet found distinct quantities of leucin in the gastric juice and mucous membrane, and obtained chloride of leucin by treating an infusion of mucous membrane with hydrochloric acid. If the mucous membrane is exposed to the air for only a short time, sarco-lactic acid is formed from it by a sort of fermentation. These experiments were made with gastric juice from a gastric fistula produced by operation in a man, so that the absolute purity of the juice is difficult to prove, and the admixture of organic acids arising from food was not excluded with certainty. I have, nevertheless, wished to quote these investigations of M. Richet, because they will probably serve as a point of departure for further inquiries. Their importance is, that they prove in a new way that fresh gastric juice contains only one mineral acid. The hypothesis that it is present as chloride of leucin must at least remain doubtful. For the purposes of strong digestion, free acid is indispensable. Admitting that chloride of leucin is decomposed at the commencement of digestion, yet some one before Richet must have found such an easily demonstrated body as leucin in vomited matter and fresh gastric juice. Certainly Kühne and Uffelmann long ago, and before Richet, proved the existence of leucin in the gastric mucous membrane and gastric juice; but it was regarded by both, from the place in which it was found, as an accidental admixture.

The amount of hydrochloric acid contained in the unmixed human gastric juice harmonises with the above-mentioned statement with respect to the dog, to 3 per mille according to Szabo, while Richet gives 1.3—1.7 as the mean of seventy observations. His investigations were made on a patient

who had had gastrotomy performed for an impermeable stricture of the œsophagus.

There still arises the interesting and hitherto puzzling question, what are the causes that bring about the secretion of acid, and, moreover, of a mineral acid gastric juice from the alkaline blood? A brilliant experiment of Maly's has thrown an unexpected light upon this. There are fluids of alkaline reaction which may contain two acid and alkaline mutually inoffensive salts, but still have an alkaline reaction, because the acid reaction is to a certain extent eclipsed: for instance, a solution of neutral phosphate of soda ($Na_2\,H\,PO_4$) and acid phosphate of soda ($Na\,H_2\,PO_4$) is alkaline. Such a solution placed in a dialyser after a short time gives up its acid salt to the surrounding distilled water, and one has in the dialyser an alkaline fluid, outside an acid fluid. M. Maly proved that in blood, in spite of its alkaline reaction, acid phosphate of soda as well as free hippuric and uric acids are present. These acids and acid compounds have a greater diffusive power than the neutral salts. Hence the excretion of acid urine from the renal parenchyma is analogous to the action of a dialyser. Further, if we mix together neutral phosphate of soda with calcium chloride ($Ca\,Cl_2$), we get calcium triphosphate, sodium chloride and free hydrochloric acid, as in the following equation:

$$2\,Na_2\,HPO_4 + 3\,Ca\,Cl_2 = Ca_3\,PO_4 + 4\,Na\,Cl + 2\,HCl.$$

According to the harmonising statements of Pribram and Gerlach, lime ($Ca\,O$) is present in the blood, and therefore allows an opportunity for the formation of free hydrochloric acid. Hydrochloric acid possesses a high diffusive power—it goes three times as quickly through the dialyser as common salt; and this explains how, once formed as above in the blood, it may pass into the gastric juice in such distinct quantities as in fact we find it to do. The facts that we secrete acid urine and gastric juice are meanwhile di-

vested of their strange characters by the aid of a simple process of diffusion; but the question why phosphatic salts are only diffused in the kidney, and hydrochloric acid in the stomach, and that indeed only periodically, must be left for the future to answer.

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LECTURE VI.

GENTLEMEN,—As you know, there is in the gastric juice and glands a ferment, pepsin, the action of which on albuminous matter will occupy us more fully. I omit to enter into the methods that aim at its pure production, because none has yet completely attained its object. We obtain a ferment mixed with other matter when a glycerine extract of gastric mucous membrane is treated with alcohol in excess. A white precipitate falls, which on drying forms a white powder. This is soluble in water, and has the characteristic pepsin action. It can be heated to 100° without losing this. The preparations in common use, German and French pepsin, pepsin-ptyalin, &c., are only mixtures containing more or less pepsin or ferment, albuminoids and starch. I have analysed a number of these preparations which were accessible to me, and have given the results in the Appendix. Ebstein and Grützner have succeeded in showing that the glands contain no pepsin, but only an early stage of it, a pepsinogenous substance, which by itself is inactive without the addition of an acid to the albuminate, but by treatment with salt or hydrochloric acid it is converted into pepsin. If we extract a gastric mucous membrane with glycerine, only the pepsin passes into the extract, but not the pepsinogenous substance, whilst watery non-acidulated infusions of the mucous membrane contain

both pepsin and the pepsinogenous substance. Meanwhile we can obtain a pepsin extract mixed with many other substances by carefully washing the minced mucous membrane dissected off the muscular coat, of a fresh pig's stomach, either by the old method given by Eberle in 1834, by infusion with a three per mille solution of hydrochloric acid, or, according to v. Wittich, with glycerine, or, after Erlenmeyer, with a saturated solution of salicylic acid or formic acid solution (1 : 1000 sp. gr. 1.205). All are very practicable; the best, according to my experience, being the two first named. The glycerine infusion has the advantage of the greatest strength and easiest preparation. If we want to eliminate the impure matter as much as possible, the mucous membrane must be treated previously with strong alcohol, which does not touch the pepsin, but precipitates a part of the albumen and lixiviates the salts. I allow 500 ccm. of glycerine to a pig's stomach. It remains in this a day until the glycerine extract is active. Then it must be filtered through a fine cloth, and we obtain an extract almost as clear as water, which may be employed internally, with suitable restrictions, in doses of one tea-spoonful and more. Diarrhœa may occur as an unexpected result, and I have seen this frequently in children. The preparation of a fresh infusion is so easy, that the fresh extract should always be employed when trustworthy artificial preparations are not at hand.

The specific action of gastric juice, or, what is the same for this purpose, the pepsin or pepsin extract in acid solution, asserts itself by a definite action on albuminoids, which are converted into a modified form, the so-called peptone of Lehmann. The tangible practical object, if I may so express myself, of this change is to form out of a little diffusible body (albumen) one easily diffusible (peptone), which is capable of absorption through animal membrane in a higher degree than ordinary albumen. In fact, Funke has proved that the endosmotic equivalent of albu-

men is over 100, and that of peptone 7.1—9.9, that is, about 12 times more of the latter than the former would pass through the septum; and Acker saw that peptone solution may be forced under a certain pressure more easily through an animal membrane than ordinary solution of albumen. If we add ordinary albumen, or, better, well-washed blood fibrine, to a dilute solution of hydrochloric acid, in a short time it undergoes hyaline swelling, and forms, if only a little acid solution has been used, a compact, jelly-like mass. A part of the albumen becomes dissolved and forms the so-called syntonin or acid albumen, which is precipitable again in the form of a white precipitate, by neutralising the decanted acid with dilute soda solution. But if we add to the mixture of fibrine and hydrochloric acid solution some pepsin or pepsin extract, and keep the whole some time at the body temperature, the fibrine is dissolved, the mixture becomes quite clear, and we find at the bottom of the glass a mass of undissolved albumen, varying in quantity according to the time of the action and the relations between fibrine, acid, and pepsin. By neutralisation of the clear fluid, syntonin is precipitated in small quantity, but this is dependent upon the just-named relations. The filtrate of these forms a solution of peptone, certainly still very impure, but which possesses the following characteristic properties of pure peptone: 1. It does not coagulate on heating. 2. It gives a purple violet colour with copper sulphate in alkaline solutions, which, contrary to many statements, is distinguished very sharply from the pure violet colour of ordinary soluble albumen when treated in the same manner. 3. Treatment with acids or alkalies or salts of the heavy metals produces no precipitate. 4. The xanthoprotein reaction and the reaction of Millon give no result. 5. Mercurial salts, picric acid, tannin and gallic acid, give no precipitate.

It is very difficult, if we do not employ a very specially minute method, to obtain pure peptone solution, so that it

has been rather arbitrarily suggested as a criterion of it that pure peptone solution, when treated with strong acetic acid and ferrocyanide of potassium, gives no precipitate. If we treat such a solution with alcohol, peptone is precipitated, and after prolonged digestion there remains a residue which consists of leucin, tyrosin and other products, to be described hereafter. The process is exhibited most distinctly in the following table, in which the substances in brackets indicate the precipitate.

Albumen + gastric juice (pepsin or extract + hydrochloric solution) prepared and digested at 37° 5. The solution is neutralised with soda and filtered :

Syntonin

Peptone solution.

Afterwards precipitated with alcohol and filtered :

Peptone

Leucin, tyrosin, &c.

The peptone precipitated by alcohol, as I have represented in the diagram, is not at all a pure preparation, but is contaminated with all the residue of albumen, pigment, fat and salts, according to the purity of the albumen originally employed and the duration of the chemical operation, which is given here only in its general outlines. Pure peptone must depart in its composition as little as possible from the albumen originally employed for digestion, and such a preparation is so hard to produce, that different investigators who have occupied themselves with this substance have claimed quite different substances for pure peptone, and have given correspondingly diverse definitions of it. But it can have no interest for us to trace these investigations, as

Henninger has recently claimed to have produced pure peptone. Whilst, then, the analyses of the bodies earlier found and described as peptone depart most importantly from the composition of albumen, he prepares peptone which, as this table shows, very nearly corresponds to the albumen employed in digestion.

	Peptone.		Fibrin.
	I.	II.	
C	51.58	51.29	52.51
H	7.02	7.08	6.98
N	16.66		17.34

The substance prepared by Henninger is white, amorphous, easily pulverised, without smell or taste, dries at 118°, and decomposes at 160°–180° into water and ammonia. It dissolves in water and acetic acid, and gives the above-named reactions. According as the peptone is prepared from serum, albumen, casein or fibrin, there are small differences to be observed, especially in its relations towards polarised light, which all peptone solutions turn to the left.

What are these peptones? What position do they take among the albuminoids?

Adamkiewicz has endeavoured to maintain, on the basis of a very able investigation, that chemically they are nothing but albuminates, which differ from the ordinary albumens by containing rather fewer salts and a somewhat different molecular formation. One of the characteristic properties of a solution of peptone, its unchangeability by heat, occurs, according to A. Schmidt and Aronstein, in ordinary albumen which has been deprived of its salts by diffusion. But, on the other hand, the fact that such albumen becomes again coagulable on the addition of salts, which is certainly not the case in peptone solutions, contradicts Adamkiewicz' views. Moreover, Henninger maintains that by a proper procedure the saline constituents of an ordinary albuminate may be made easily less than those in peptone, without the thus

altered albuminate having the characteristic properties of peptone.

But the chief point is, that Adamkiewicz had as little as his predecessors to deal with pure peptone, so that his argument and conclusions may be, so to speak, ruled out of court.

In opposition to this theory of Adamkiewicz, Hoppe-Seyler makes it very probable that peptone is formed out of ordinary albumen by taking up water, quite analogously to the formation of grape sugar out of starch. Henninger has directly proved this by comparing the composition of his pure peptone with the albumen originally employed; and besides, he performed the experimentum crucis, as he could change his peptone back again, by abstracting water (heating with anhydrous acetic acid at 80°), into a body which had all the properties of syntonin, that is, the next modification of fibrine. Hofmeister obtained the same result by heating fibrine peptone to 140°—170°, and it appears from this that the proposition *that peptone is to be regarded as the hydrate of albuminate* will form a durable and valuable addition to our knowledge.

Besides its peptonising property, gastric juice, as you know, also possesses that of effecting the curdling of milk. In the preparation of whey, this has the most extensive employment, as the so-called rennet is nothing but gastric juice, or rather gastric juice imbibed by the gastric mucous membrane. Hammarsten has succeeded in isolating from gastric juice a body differing from pepsin, which effects the coagulation of milk in neutral or acid solutions without changing the reaction. He describes it as the rennet ferment. But in milk there is milk sugar, which by treatment with gastric juice is partly converted into lactic acid, and remains unchanged when treated with Hammarsten's rennet ferment; so we have nothing to oppose to the further conclusion of Hammarsten, that besides the "rennet ferment" there also exists in the gastric juice a "lactic acid ferment,"

if we provisionally accept the simple facts, without regarding the question as to whether these actually are ferments, as finally settled.

The action of the gastric juice or acid pepsin solutions should be, according to the theory of ferments, quite endless—that is, able to convert any quantity of albumen into peptone. But this is not the case. In an artificial digestive mixture, the process comes to a stop after a certain time, before all the albumen is digested. We must then add more acid. In what manner the acid is utilised has not been hitherto satisfactorily explained. According to Hoppe-Seyler, it forms acid compounds with the albuminoids present (syntonin and peptone). Finally, the addition of acid no longer helps in the digestion of further quantities of albumen; the pepsin becomes inactive, probably decomposed. The necessary quantity of pepsin, compared to the quantity of albumen finally digested, is always surprisingly small, and this circumstance, added to the above proof that peptones are formed by the hydration of albuminates, supports the belief that pepsin is a true ferment, in spite of the theoretical claims not being, as we saw, completely satisfied.

The necessary amount of hydrochloric acid in digestive fluids fluctuates within proportionately wide limits, and lies between 0.1 and 5—7 p.c. Moreover, it is not equal for all kinds of food, as we know from the researches of Wawrinsky and Brücke. Fluid albumen is more difficult to digest in feebly acid fluids than solid albumen, whilst the reverse occurs with higher (normal) degrees of acidity. We know besides that we can digest artificially not only with hydrochloric acid, but also with phosphoric acid, sulphuric acid, acetic acid and lactic acid, but that the active degree of acidity varies with the acid employed. Davidson and Dieterich in 1860 showed by comparable observations that the same digestion requires with lactic acid about six times higher acidity than with hydrochloric acid, and about half as much again as with acetic acid; 100 grms. of fresh gastric

juice dissolve five grms. of dried albumen, according to Lehmann; according to Bidder and Schmidt, 2.2 grms.; according to Corvisart, 4.9 grms.

The *rapidity of digestion* is nearly proportional to the temperature, and is best at from 37° to 40°, the variations being dependent upon the mechanical action of the movements of the stomach. Artificial digestive mixtures decompose and dissolve all the quicker when they are shaken from time to time. The condition of the albumen is also of importance. Blondlot saw that a dog with gastric fistula digested 100 grms. of boiled albumen in five hours, 100 grms. of albumen beaten to froth in three and a half hours. Uffelmann gave a boy with a gastric fistula a solution of albumen and water, and could prove the existence of peptone after twenty minutes; therefore the statement that hard-boiled eggs are digested better than soft, certainly originates in an error. Wherever albuminoids are taken as constituents of our complexly-formed nutriment, their rapidity of digestion depends naturally entirely upon the condition of the nutriment, that is, its accessibility to the gastric juice. Here is a table in which you will find these conditions arranged, as they are of the highest importance for us as practitioners. (See Appendix.) Neutralisation of the gastric juice or admixture of bile stops digestion. The latter, according to Burkart, forms a precipitate by means of the bile acids, which mechanically throws down the pepsin; certainly it would need for that a great quantity of bile. A little bile allows the digestion to continue, as you may perceive here. It appears to me doubtful whether the pepsin digestion stops at once in the contents of the stomach in the duodenum, from the action of the bile. The gastric digestion is hindered or prolonged by all salts of the heavy metals (acetate of lead, mercuric chloride, &c.); hence the well-known rule to administer these considerably before or after meal-times. Alcohol, carbolic acid and concentrated solutions of alkalies, have a similar influence, be-

cause, partly by irritating the mucous membrane, they give rise to an alkaline transudation into the stomach. The much-prized bitters and carminatives, according to Buchheim, do not further digestion, while spices, on the contrary, as is well known, stimulate secretion. Heating destroys the action of the gastric juice, but freezing does not. I have repeatedly evaporated to a small volume on the water-bath a watery gastric juice of the dog, which was obtained by pumping it out from the living animal, and then proved its peptonising action, while glycerine extract from the pig's stomach does not usually become inactive by heating and treating with water. The digestive mixture which I show you now was prepared with a glycerine extract so treated. You see in the filtered solution the characteristic reaction of peptone, and perceive besides that even higher temperatures, as previously described, do not make the ferment inactive.

Finally, just a word or two on the place of secretion in the stomach, that is to say, whether only the fundus or also the pyloric region secretes active juice. There has been a great dispute waged on this subject, which we happily can pass over, because it is decided by the following experiment of Heidenhain's: Separate the entire pyloric region, preserving the mesentery and vessels from the stomach, bring together the remainder of the stomach and the duodenum, and form a sort of pouch in the abdominal wall out of the separated piece. In the dogs which survive this terrible operation, there forms a fistula which secretes a thick hyaline mucus, which, treated with 0.1 p.c. of hydrochloric acid, digests fibrine vigorously, and curdles milk without forming any acid. But, as you may perhaps recollect, the pyloric glands possess only the "so-called fundamental cells;" so this experiment pleads in favour of the many times disputed view, which Heidenhain has supported by other arguments and by the microchemical relations of the cells and their different resistance to dilute hydrochloric

acid, that we have in the fundamental cells the pepsin-secreting, and in the pavement cells the acid-secreting part of the gland. The thick mucus which covers the surface of the stomach is derived, and especially in the pyloric region, from a mucous metamorphosis of the epithelium.

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v. Wittich. Ueber eine neue Methode zur Darstellung künstlicher Verdauungsflüssigkeiten. Pflüger's Archiv. Bd. ii. p. 192.

Erlenmeyer. Darstellung der ungeformte Fermente. Münchener Sitzgsber. mathem. physical. Classe. 1875, Hft. 1, und Ztschrft. f. analyt. Chemie, Bd. xv. p. 426.

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Hammarsten. Ueber die Milchgerinnerung und die dabei wirkenden Fermente der Magenschleimhaut. Jhrsber. f. Thierchemie für 1872, p. 118.

Blondlot. Traité analytique de la digestion, p. 270.

Uffelmann. Loc. cit.

Heidenhain. Ueber die Pepsinbildung in den Pylorusdrüsen. Pflüger's Archiv. Bd. xviii. p. 122.

Wawrinsky. Ueber die Löslichkeit des geronnenen und flüssigen Eiweiss im Magensaft. Jhrsber. f. Thierchemie, 1873, p. 178.

Ebstein and Grützner. Ueber Pepsinbildung im Magen. Pflüger's Archiv. Bd. viii. p. 122.

Witt. Einige Untersuchungen über den Ursprung des Pepsin. Jhrsber. f. Thierchemie, 1875, p. 160.

LECTURE VII.

Gentlemen,—Besides the above described fluid matters, the stomach always contains more or less gas, which consists in part of air swallowed, in part of carbonic acid which proceeds, according to Lehmann, by diffusion from the blood. Planer found in a dog, five hours after feeding, 25.2 volumes p.c. CO_2, 68.68 N, 6.12 O. But according to Strassburg, the carbonic acid tension of the arterial blood is at the highest 4—5 vols. p.c., so that the carbonic acid found by Planer could not have proceeded from the blood, but must have been generated in the stomach or intestine. Air is not only carried into the stomach by swallowing, as is certainly proved, but also by coughing or by forced respiration. With the help of a wire œsophagus sound which served as the electrode of a thermal element, I have measured the temperature of the stomach under different conditions. With every inspiration I observed a diminution, which ceased when the subject of the experiment breathed air at the temperature of the body. How far, under normal conditions, the œsophagus allows air to pass by means of the variations of expansion undergone by the stomach in consequence of the abdominal pressure, I dare not venture to say, as in œsophagotomy we find the lumen of the œsophagus firmly closed.

In diseases of the stomach, which induce either an unusual formation of acids or an abnormally long sojourn of

food in the stomach, the ingesta easily undergo *fermentative decomposition.* The hydrocarbons decompose in the last instance in part to form gas. In consequence of the presence of ferment-exciters—which we have seen are always brought from the outside—they develop either the so-called alcohol and acetic acid fermentation, or the lactic acid and butyric fermentation. The first careful exposition of these relations we owe to Frerichs, whose acuteness transferred the employment of fermentation equations to pathology. In the following table you have before you the steps of the fermentations in question, and you will at the same time bear in mind the organisms which give rise to them.

$C_6 H_{12} O_6$ Sugar

$2\,(C_2 H_6 O)$ Alcohol $+ 2\,CO_2$	$2\,(C_3 H_6 O_3)$ Lactic acid
$C_2 H_6 O + O = C_2 H_4 O$ (Aldehyde) $+ H_2 O$	$C_4 H_8 O_2 + 2\,CO_2 + H_4$
$C_2 H_4 O + O = C_2 H_4 O_2$ (Acetic acid)	(Butyric acid)

Schultzen and Wilson have shown that many forms of fermentation may occur together. I had the opportunity, in company with my lamented colleague Rupstein, of observing a case in which, as the patient very pithily observed, "there was sometimes a vinegar factory and sometimes a gas-works in his inside." In the one case the alcoholic fermentation led to the formation of acetic acid, in the other the butyric fermentation produced hydrogen and carbonic acid. This patient was specially remarkable, as he at times belched higher hydrocarbons, such as Marsh gas, and (perhaps) Olefiant gas, which took fire when a light was held in front of him, and burnt with a faintly luminous flame. In this case there must have been present still another fermentation, that of marsh gas. Hoppe-Seyler thinks marsh gas might be regurgitated out of the intestine. Since we know from this observer that an active development of marsh gas takes place from cellulose in sewer mud, it appears to me that the formation of this gas in the stomach is quite possible. A connection between the different fermentations and the kind of food

was not proved. The man died later on, and we found that he had not, as we imagined, a dilated stomach, but a flat scirrhous tumour of the pylorus. The shape of the tumour accounted for it not being detected by palpation, but it caused decided stricture of the orifice. The question of the *self-digestion of the stomach* is of very special interest for us as practitioners with respect to the production of gastric ulcer. The famous experiment of Bernard—the leg of a living frog thrust into the opening of a gastric fistula in a dog becomes digested, or rather injested—is easy to repeat, especially with a curarised frog. The cadaveric softening of the stomach, that is self-digestion, is indisputable. On the other hand, Leube has very lately shown that pieces of mucous membrane may be torn off in sounding or washing out the stomach without any harm resulting.. Considerable hæmorrhages into the stomach, obviously from large vessels, occur in many acute febrile diseases without any bad result. Gastric ulcers themselves occur without any definable cause, and extend in breadth and depth very slowly under certain conditions, or frequently heal completely. There is one explanation of this : whenever living blood circulates in the mucous membrane under normal pressure, the gastric juice has no point of attack. But where the normal blood nutrition ceases, either in consequence of embola (Virchow) or of ligature of vessels (Pavy), and necrosis of tissue occurs, there, as elsewhere, the gastric juice digests the dead tissue. Simple hæmorrhages, without distinct fall of blood pressure and slowing of the circulation, are not sufficient, as is evident from many instances of benign hæmorrhages.

Koch and I, starting from a statement of Schiff's, that certain injuries of the central nervous system are connected with gastric hæmorrhages, divided the cervical cord, or the adjacent portion of the dorsal cord, in six dogs, to produce hæmorrhages in combination with diminished blood pressure. As a fact we obtained, in those animals which survived longer than 36 hours, numerous lenticular gastric ulcers,

which were mostly circular "and as if punched out," going deeply into the submucosa. With the microscope we could see evidence of hæmorrhage out of the vessels of the mucous membrane between the glands, and in the entire area of the effused blood the elements of the mucous membrane, gland tubules and connective tissue, were digested deeply down in the shape of a funnel. No traces of inflammatory processes were to be found. It produced also typical gastric ulcers; and it needs only a glance at the stomach and the preparations which I show you, to recognise the correctness of my statements. The administration of acids or purely mechanical lesions do not cause, as we must maintain in opposition to Pavy, any ulceration. Why these hæmorrhages occur, and why only precisely in the gastric mucous membrane, is quite obscure. As we could not attain our object, that of explaining perforating ulcers, we refrained from publishing the particulars of the experiments. In opposition to the above-quoted experiment of Bernard's, the carefully shaved foot of a living dog was kept for six hours in a mixture of glycerine gastric extract and hydrochloric acid at the body temperature without being at all affected. Our experiments agree with those of Virchow and Pavy, as it was only when innutrition of the mucous membrane occurred as a consequence of entire or partial interference with the circulation that ulcerative digestion resulted. This is the reason why ulcers remain so long stationary, and increase so slowly in depth and breadth.

When we come to consider the influence of pathological changes on the secretion of the gastric juice, in accordance with the observations of Beaumont and the experiments of Manassein, fever must be placed in the first rank. In fever, from whatever cause, the gastric secretion does not indeed cease, but obviously a less active juice is secreted. My own experience enables me to confirm this in the most complete manner with respect to the human subject. If we wash out with an equal quantity of water the fasting stomachs of two

individuals, one healthy and the other suffering from fever, after having given to each of them, for the purpose of stimulating temporary secretion, a little tinct. capsici, and submit an equal quantity of albumen to the action of an equal quantity of filtered stomach extract from each of the cases, we find that the gastric juice from the fever case digests much less, or at least much more slowly than that from the healthy person. The reaction is usually acid, rarely neutral: I have never met with an alkaline reaction. So that we can, as Hoppe-Seyler points out, strengthen digestion by adding hydrochloric acid. This confirms the old practice of prescribing phosphoric or hydrochloric acids in fever mixtures. The diminution of the pepsin digestion is not in all cases equally great, or indeed present at all. Uffelmann observed in a gastrotomised lad who had chronic fever rising to 39.2° (102.5° F.), that, as above remarked, albumen solutions were converted into peptones after twenty minutes, and the boy increased 18—19 p.c. in weight in the course of twelve weeks' fever. In an epidemic of diarrhœa, the same observer examined the vomit of the patients, and found at first, in spite of the fever, that it was actually more acid than normal; but later on the reaction changed suddenly to alkaline simultaneously with the discharge of slimy bilious masses, and—always an unfavourable sign—the digestive powers thenceforth completely disappeared. On the other hand, the gastric contents sometimes have an alkaline reaction, of course apart from the effects of medicine. This occurs when a strongly alkaline transudation is poured out into the stomach in connection with diminished or entirely abolished secretion of acid.

I will give you, Gentlemen, an easily-performed method for estimating the reaction of the gastric contents sufficiently for practical purposes. To a definite portion of gastric contents filtered, or rapidly strained through a fine cloth, add a few drops of alcoholic solution of rosaniline. The fluid becomes violet with an alkaline, and yellow with an acid

reaction. Then add to this solution small quantities of a 1 p. c. solution of soda or hydrochloric acid, by means of any convenient measuring apparatus, until the reaction is reversed and the contents are converted to acid or alkali in a definite and, for future estimations, comparative degree. An indispensable requisite is obviously to work always under conditions as equal as possible, during fasting, using equal quantities of water for washing out, &c. Even then we attain only approximate results. The simple fact of acidity in itself does not prove that either the right acid or the right degree of acidity is present. Acetic acid, lactic acid, butyric acid, may make the gastric contents acid, and nevertheless one must prescribe acid under such conditions, because the active degree of acidity for the last-named acids, which is, as we have seen, very high, has not been reached. Again, by salicylic acid we can at the same time produce an anti-fermentative and a digestive-promoting action. But there is a second change in the gastric secretion, which I might call the relative change. It occurs when the secreting part of the mucous membrane is quite efficient, but is diminished relatively to the ingesta by pathological processes (new formations, ectasis). Thus there are cancers the symptoms of which are those of chronic dyspepsia. In dilatation of the stomach there is more food collected in the organ than the gastric juice can manage, because, as I have proved in a relatively large number of such stomachs, the gland tubules are not increased, but in parts, indeed, are atrophied, and the dilatation is brought about simply by stretching of the connective tissue and the deposit of a small celled infiltration. Such cases of "relative insufficiency of secretion" are those which especially demand the employment of artificial digestive preparations. But ordinarily in dyspeptic conditions, as I have said, it is not the pepsin which is wanting, but the derangement originates in the absence of the required degree of acidity. If acetic or lactic acid have formed in the stomach, if the secretion of the normal gastric acid, as it frequently is,

be suppressed or diminished, the reaction is very acid, and yet not enough acid is present to effect proper digestion. As we have seen, digestion with lactic acid requires nearly six times the degree of acidity that hydrochloric acid digestion needs. This is my experience obtained in practice, and it receives great support from the fact that Hoppe-Seyler, from work done in his laboratory, has come to the same conclusion.

If we desire to examine the chyme, the product of digestion, we do not need the experiment of Gosse, who by swallowing air could vomit his stomach contents at any time, or have recourse to some emetic. We may study it in gastric fistulæ or by the aid of the stomach-pump. Allow me here to describe only some single typical constituents. With respect to the greater or less solubility or digestibility of particular articles of diet, I must refer you to the tables in the Appendix.

Muscular tissues are dissolved more or less rapidly, according to the resistance of their perimysium, their fasciæ, and their accompaniments of fat and tendon, until the gastric juice has only the fibrillæ themselves to deal with. Fat meat is much harder to digest than lean, old than young, raw than cooked. These differences depend upon the solution of the fibrous stroma by cooking and the digestion in the acid gastric juice. The proper pepsine digestion is probably equally rapid for all muscular fibres. They are decomposed into their primitive bundles, and these into a granular mass, in which their finer structure cannot be recognised. Frerichs says that muscular fibre is never completely dissolved in the stomach; and in fact we find numerous unchanged fibrillæ in the small intestine, as I have recently described in a case of præternatural anus.

Gelatine and gelatine-yielding tissue (cartilage and bones) are very hard to digest. If the gelatine is extracted from the bones, it is changed, according to Uffelmann, into a substance very like peptone and sugar. This result of Uffelmann's investigations is all the more welcome, as a long

controversy has been waged concerning the fate of gelatine in digestion. Gelatine is very like peptone in its reactions. It does not coagulate on heating, is not precipitated by acids, turns polarised light to the left, but it gelatinises in the cold, and diffuses scarcely at all through animal membranes. Frerichs, Kühne, and Etzinger maintain that the gastric juice abolishes the capacity of gelatine to gelatinise, and according to Hoppe-Seyler it is almost entirely soluble in acids. Uffelmann observed that gelatine, swollen in water, after a long stay in the stomach no longer formed jelly, but diffused easily. It thus approximates very closely to true peptone, with which it agrees also in some of its reactions with precipitating agents. In fact, gelatinous substances become well digested. I can, from my own experience, confirm the good results of the gelatine mixture proposed by Senator as a fever diet.

Milk becomes coagulated and its fat in part included in the coagula; the casein then peptonises. The latter does not occur if the coagula are removed too quickly, as we see in the well-known white lumps in the diarrhœic or dyspeptic stools of children, which are formed of nothing but fat and casein.

Vegetables, so far as their envelopes of cellulose permit, are easily dissolved and digested. Gums, according to earlier views (Frerichs, Gorop-Besanez) are not digested. Voit and Uffelmann, however, state that gums and cane sugar are converted into grape sugar.

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LECTURE VIII.

GENTLEMEN,—The stay of the chyme in the stomach cannot be stated in precise figures, because the observations respecting it differ widely. Moreover, those on men were made in cases of fistula, in which some pathological influence may have been present. We only know that the stimulus which different ingesta create on the movements of the stomach and the closure of the pylorus, vary according to mechanical and chemical conditions, so that the pressure under which the chyle exists in the stomach is not only, as above remarked, dependent on the muscles of respiration, but directly and in a variable manner upon the contraction of the wall of the stomach. Uffelmann introduced, in such a manner as to be air-tight, a sort of pressure-tube through the fistula into the full stomach of his boy, and saw that the level of the fluid in the tube stood in a varying manner at 2—8½ cm. over the fistulous opening, and showed, in addition to respiratory variations of only a millimetre or so, great risings and fallings which occupied about one minute. These secondary movements are obviously to be regarded as the expressions of the peristaltic contractions of the stomach. But besides this, the fluid in the tube diminished, that is, its level sank gradually lower and lower as the opening of the pylorus (and the absorption of the fluid contents) caused the contents of the stomach to grow less. In general,

the food remains from one to six hours in healthy stomachs, but under pathological conditions much longer. On washing out the stomach, we often find undigested remains which must have lain all day in the stomach. I cannot recal who relates the case in which, during the washing out of the stomach in the spring, grape seeds were found which the patient evidently had not swallowed later than the previous autumn. In healthy dogs we often find the pieces of meat given them on the previous evening still in their stomachs at the following noon, whilst rabbits' stomachs generally do not become empty even after very long fasting.

Finally, it is unknown by what means the pylorus is opened. Busch, in his case of duodenal fistula, saw remains of food swallowed the previous evening appear the next morning, and thinks that the pylorus is generally shut during the night. Many see in the increasing acidity of the stomach the cause of the opening of the pylorus. Kretschy found the maximum acidity in a case of gastric fistula at the seventh hour after eating, and observed, coincidently with the emptying of the stomach, as might be expected, a rapid fall to a neutral reaction. It is clear that in this case the maximum acidity and the opening of the pylorus have no causal relations, as has been assumed. The fact is, that one and the same kind of food remains a very varying time in the stomach. Magendie found the gastric contents of horses, fed with equal quantities, varied in equal times after feeding from 1—5 litres. Here, obviously, psychical influences play an important part. These are conditions which in practice often enough play a not very easily determined part, and which find their anatomical basis in the connection of the vagus with the cerebro-spinal centres on the one hand, and the solar plexus on the other.

We pass now to the consideration of the *digestion in the small intestine.*

The older authors saw in the small intestine nothing more than a drain-pipe for the chyme, in which the chyle was

precipitated by the bile, and in which fat was dissolved and the useless residue passed on for defæcation. We may, without vanity, regard with satisfaction the abundance of new facts which the restless spirit of inquiry of the last decade has disclosed concerning this important subject. Let us commence with the *analysis* of the liver secretion.

I will shorten my task by abstaining from any detailed description of the minute structure of the liver, for which I refer you to the new text-books of Histology. I am permitted to do so, not only from the fact that histology still owes us the answers to the cardinal questions concerning the origin of the bile-ducts, the endings of the nerves, &c., but mainly because the recent investigations concerning the functions of the liver and the part they play in the organism as a whole, have shown most conclusively that the balance inclines much more to the side of general metabolism than to that of the digestive functions. When we hear that dogs with biliary fistulæ, appropriately treated and nourished, remain alive a long time without injury to their general health; when we remember that biliary fistulæ in men, as in the observations of Fouconneau-Dufresne, Walter, Oppolzer, &c. (quoted by Frerichs, Leberkrankheiten), exist for years; that cases of the deepest jaundice may recover without notable injury to the general health,—we are sorely tempted to repeat anew, but in reference to digestion, the humorous epitaph with which Bartolinus denied to the liver the Galenic rôle of the blood-preparing organ: "Siste viator, clauditur hoc sub tumulo, qui tumulavit plurimos," &c.

But it is not so; and Blondlot was wrong when, from his observations on dogs with biliary fistulæ, he denied to the bile any share in the work of digestion. The bile has a definite effect in digestive action, but its absence may be compensated for, and, as we have seen, for a long time, by the vicarious action of other secretions. The liver is, from its containing insoluble glycogen, the mighty storehouse of hydrocarbons for the organism, out of which the blood and tissues are pro-

vided as required with grape sugar, just as insoluble starch is deposited in the seeds of plants, which is changed by diastase into soluble sugar and then employed in the nutrition of the cells. It is also the secreting organ for a series of materials circulating in the blood and consumed in the liver, the accumulation of which in the blood, after destruction of the hepatic function, acts poisonously; and it becomes thereby the place of origin of a number of substances which pass in part as urea into the blood, in part as the constituents of bile into the intestine.

But a series of facts indicate that by the formation and excretion of bile we are to perceive much rather the *elimination* from the blood of certain early stages of bile than an essential aid to digestion. The liver has a double rôle. It is a secreting and a storing organ, and its use in digestion, so far as the action of the bile is concerned, is subordinated throughout to the other function. In the pathology of the liver, the absent or altered bile has almost no effect on the digestive process; but it is the derangement arising in the general metabolism which gives rise to the severe symptoms of liver diseases. But I can only indicate these relations, the discussion of which would lead us too deeply into the region of tissue metabolism, to be consistent with my intention to limit myself to the description of the constituents of the bile and its secretion.

Let us pass on to the description of the bile.

Biliary fistulæ secrete a golden yellow or yellowish green, clear, slightly tenacious secretion of intense bitter taste, feebly alkaline reaction, and a sp. gr. of 1.026 to 1.032—the *bile*. Its quantity increases with digestion, reaches its maximum in the fifth to the eighth hour after food, and then falls again; but the secretion never ceases entirely, except under pathological conditions. The secreting function is here, as elsewhere, dependent upon the circulation, as the ligature of all the hepatic vessels causes complete stoppage of the biliary secretion. The ligature of the portal vein, with the

artery left untied, permits the occurrence of a short continuance of secretion. Slowing of the blood-current in the portal vein, which occurs after stimulation of the vagus as an indirect consequence of slow respiration, and the initially increased blood pressure, causes, according to Heidenhain, a transient increase in the secretion. After diabetic puncture in the floor of the fourth ventricle, B. Naunyn found slowing of the biliary secretion, no doubt as the consequence of the altered vasomotor innervation of the liver, and the resulting diminution in the blood pressure in its vessels. It is possible that these and similar consequences arise in part from the contraction of the smooth muscular fibres of the bile-ducts. Thus a reflex contraction of the bile-ducts occurs when the acid chyme touches the papilla of the ductus choledochus, and Schiff suggests that the chyme as it passes is played upon by a jet of bile. But the whole subject needs more data, and those we have are as uncertain as those concerning the quantity of bile secreted. Thus J. Ranke observed a man with a hydatid of the liver which had ruptured into the lung, who coughed up in 24 hours 652 grms. of bile, but this varied from 145—945 grms. Wittich found in a woman with a biliary fistula 552 grms.; Harley, 600 grms.; Westphalen, 453—566; in dogs, much higher figures are given. The bile formation often appears to be quite suppressed; at least cases are described, as that of von Stabell, in which complete decolorisation of the fæces occurred without jaundice. The action of drugs on the secretion of bile has been studied on an extensive scale by Rutherford and Vignol, and on account of the practical importance of these investigations I have summarised their results, together with some other observations. (See Appendix.)

The composition of the bile may be seen in the following two tables. The first is the mean of two very nearly equal analyses of Frerichs and Gorup-Besanez, which were obtained (1) from a young man of 22; (2) from a man aged 49 (decapitated). The second gives, according to Hoppe-

Seyler, the mean of five samples of human bile obtained post mortem, in which only the organic matters are estimated. They amount to somewhat more than half those of Frerichs and Gorup-Besanez; and Westphalen found in the fresh bile of his patient only 2.25 p. c. of solid residue, which by stagnation of the bile rose to 4 p. c. Similar variations are found in other analyses, and it is no wonder, for, as pathologists have long known, the concentration of the bile in the gall-bladder may vary greatly within certain limits.

I.	
Water	84.14
Inorganic matter	1.05
Organic matter	15.50
viz.	
Mucus and colouring matter	2.54
Cholestearin and fat	2.95
Salts of bile acids	9.96

II.		
Water		91.68
Inorganic matter		
Organic matter		8.32
viz.		
Mucus		1.29
Bile salts	Taurocholate of sodium	0.87
	Glycocholate of sodium	3.03
Soaps		1.39
Cholestearin		0.35
Lecithin		0.53
Fat		0.73

The organic constituents consist of phosphates and carbonates of lime and sodium, with potassium and sodium chlorides. Under organic matter, there are still to be named a not yet isolated diastatic ferment, and, according to Naunyn's analysis, sugar. In order to prove the diastatic capacity of bile, we must take the fresh bile of an animal just killed. After long standing the bile acts no longer. This property of bile appears to be not constant and to be slight in all cases. Frerichs overlooked it. I have not always found it, which difference I attribute, as just explained, to changes occurring on exposure to air. On the other hand, Wittich proved its presence in fresh human bile, and indeed extracted the diastatic ferment in question by his glycerine method.

We can easily perceive the mucus of the bile, quite apart from its tenacity, in cases of obstruction of the gall-ducts by concretions. There are cases of long-standing jaundice, in which the gall-ducts and the gall-bladder are filled with a pale, mucous, sticky fluid, which scarcely suggests bile. This mucin is in all probability not a product of the liver cells, but a secretion of the bile passages or their mucous glands, as the more abundantly the bile flows the poorer is it in mucus. But with slow secretion a greater absorption takes place through the walls, which may diminish the per-centage of water while increasing the mucus, so that the question as to the seat of the secretion of mucus is as little decided here as in the case of the stomach.

Let us turn to the consideration of the most important constituents of the bile, its specific acids and colouring matter, it being understood that it is not my intention here or elsewhere to enter into details of chemical methods and theories. For our present object that would be only waste of time. Therefore I pass by methods of production, chemical constitution, enumeration of general reactions, &c., and keep to the facts which are important to pathology.

In the bile there are two acids, or rather their alkaline salts, glycocholates and taurocholates of sodium and potassium. They are insoluble in ether, so that they are easily obtained from an alcoholic solution of evaporated bile by precipitation with excess of ether. The fine, acicular, silk-like crystals which you see here, have been separated in this way, and are what was described as Plattner's crystallised bile. If we prepare the acids pure, and boil them with caustic potash or baryta water, they decompose, giving up water, into one of two acid-like substances, cholic acid and another body which in this case has the character of a base. In one case, this is glycocoll or gelatine sugar; in the other, taurin. The latter is only found in bile, the former is widely distributed in the animal body. Both are nitrogenous substances and direct derivatives of albuminate. Glycocoll

is prepared directly from animal gelatine. Taurin proves its near relationship to the albuminoids by containing a considerable quantity of sulphur. It is further interesting that it belongs to the rather rare bodies in the organism which we can prepare synthetically, in this case from alcohol, sulphuric acid, water and ammonia.

$$\text{Glycocholic acid} \left\{ \begin{array}{ll} \text{Glycocoll} & = C_2\, H_5\, NO_2 \\ \text{Water} & = H_2\, O \\ \text{Cholic acid} & = C_{24}\, H_{40}\, O_5 \end{array} \right\} C_{26}\, H_{43}\, NO_6$$

$$\text{Taurocholic acid} \left\{ \begin{array}{ll} \text{Cholic acid} & = C_{24}\, H_4\, O_5 \\ \text{Water} & = H_2\, O \\ \text{Taurin} & = C_2\, H_7\, NSO_3 \end{array} \right\} C_{26}\, H_{45}\, NSO_7$$

In order to obtain the bile acids by Pettenkofer's reaction, the biliary salts must be in the purest possible solution. By adding, drop by drop, concentrated sulphuric acid to the solution treated with cane sugar, in time there occurs a gradually deepening purple coloration, provided that the temperature of the fluid does not exceed 70°. But it always is a very minute and prolonged business to separate the bile acids from the fluids to be tested, especially from urine, and therefore the following method of Strassburg is of importance for medical practice, as it enables us to ascertain the presence of bile acids in the urine rapidly. Dip a strip of filter paper into the urine treated with sugar, and dry it. A drop of sulphuric acid dabbed on the paper, in the presence of bile acids, becomes after a few seconds a beautiful violet colour, which soon becomes dark purple red, and this detects 0.03 mgrm. of the bile acids with certainty. The pathology of liver diseases has a deep interest in the discovery of bile acids in the urine. Their presence played a great rôle for a long time in the questions of hepatogenous and hæmatogenous jaundice, as it was believed that their presence in the urine was a certain criterion of jaundice by absorption. But afterwards, on the one hand, Naunyn found bile acids in the urine of hæmotogenous (pyæmia) jaundice, and, on the

other hand, Lehmann failed to find them in obstructive jaundice, so that the value of this sign became more than doubtful. It would be worth nothing if these statements were better supported; so that new and extensive observations with the help of Strassburg's method, which, as we have seen, is very easy to carry out, would be very valuable.

If we shake bile that has been exposed to the air with chloroform, this takes up a green colouring matter, biliverdin. Fresh bile, however, owes its golden yellow colour to bilirubin, which when pure is an amorphous orange yellow powder, forming, by oxidation in the air or other oxidising means, the green biliverdin (formerly called cholepyrrhin or cholephaïn). Chemists have produced a series of intermediate stages, especially biliprasin and bilifuscin, and studied their spectroscopic relations and their connections with the pigments of blood and urine, which we referred to in the first lecture. Two points especially interest us: the derivation of and tests for the bile-colouring matter. At first sight, there seems no doubt that bile pigment is derived from the pigment of the blood corpuscles, hæmochromogen. By injection into the circulation of a whole series of substances which dissolve the blood corpuscles and set free the pigment from them, we succeed in producing bile-coloured urine. Among these solvents are salts of the biliary acids, solutions of hæmoglobin, large quantities of water, chloroform and ether. The same solution may occur naturally in old blood extravasations, when, as you know, peculiar crystals (Virchow's hæmatoidin crystals) have been found, first by Virchow, later by Hoppe-Seyler, also in the margin of the placenta and in the fluids of cysts, while their identity with bilirubin has been ascertained by Jaffé. On the other hand, Funke and Zenker found the same crystals in old bile residue. Valentiner prepared hæmatoidin crystals from pulverised gall-stones, and Schwanda succeeded in extracting characteristic crystals from the urine of a case of jaundice. Neumann found bilirubin crystals in the blood of a three-days' old and

probably suffocated child. Finally, as before remarked, Hoppe-Seyler has succeeded in producing, by the use of reducing agents, from hæmoglobin a body identical with urobilin, the colouring matter of urine. This urobilin is a derivative of bilirubin, and has been prepared from it by Maly, so that the origin of bile pigment from blood pigment is in fact proved. The bile pigments are only the middle products in a series of reducing processes which convert the blood pigment into the pigment of the urine. This fact has such significance for the pathology of jaundice, that I could not pass it over, although strictly it goes beyond our proper subject. As to the rôle of the bile pigment in digestion we can say nothing, nor do we know how or in what manner it participates in the digestive process, so that I pass to the second of the above points, the reactions of the bile pigment. Respecting this I may incidentally direct your attention to a simple test suggested by Rosenbach: a large quantity of icteric urine is filtered, and the wet filter paper dabbed with a drop of impure nitric acid, at the borders of which comes the play of colours from red to green. Cholesterine (the beautiful shining crystals of which have given rise to the name "bile fat," although the body has nothing to do with fats, but is an alcohol) and lecithin are bodies about which we are in the same state of ignorance as we are concerning the bile pigment, so we shall be content to remind you of the solubility of the first-named body in solutions of biliary acids and its insolubility in water. Under certain conditions of diminution of the bile-acid constituents of the bile, cholesterine is separated in the form of gallstones.

If we inquire as to the functions of bile in digestion, the few facts we know are quickly enumerated, but their interpretation is uncertain and doubtful. Let us consider shortly what are the contents of the chyme as it enters through the pylorus into the intestine:

1. All matters still undigested by the saliva and gastric

juice, such as starch or paste, gelatinous tissues, dissolved gelatine, albumen (syntonin and native albumen) dissolved by the gastric juice but not yet converted into peptone, and the isolated, partially digested, but still not decomposed primitive muscular bundles. 2. The products of digestion up to the pylorus, viz., peptone, dextrose, levulose, peptonised gelatine. 3. All matter quite unchanged by saliva and gastric juice, fat, fatty acids, cellulose. 4. Gastric juice or fluid, with the fluid constituents not hitherto absorbed in the stomach, including mucus and gastric juice.

This entire mass possesses a strongly acid reaction. The bile has a very alkaline reaction and moderates the acidity of the chyme. Many maintain that it neutralises the chyme and precipitates from the neutral solution, the pepsin, syntonin and unchanged albumen. This is more than doubtful. If we open the duodenum of an animal killed during digestion we find—at least I have always found it so—the contents of intestine beyond the opening of the ductus choledochus still very acid; there is no trace of precipitation of albumen. In the above-mentioned case of preternatural anus I found the reaction of the secretion from the fistula in a much lower part of the gut as often acid as neutral. There can be no good in discussing whether such a precipitation occurs, for, as we shall see later on, the albuminous matter in the mass, as it is precipitated by the changed reaction, is submitted to the action of the pancreatic juice, which changes it at once into other soluble modifications.

Much more certain is a second property of bile, which it owes to the salts of the bile acids, and which concerns the emulsification of fats. A good emulsion, that is the finest possible division of the fat-drops in a more or less viscid menstruum, only occurs when the fat to be emulsified contains free fatty acids and the menstruum has an alkaline reaction. Under these circumstances, as Brücke showed, the slightest shake is sufficient to form a permanent and fine emulsion; indeed, under certain mutual relations between the

fat, fatty acids and alkali, there scarcely needs, as Gad discovered, any mechanical aid. A drop of cod-liver oil, which always contains some free fatty acids, if placed in a watch-glass with a 0.3 p.c. solution of soda, passes in a few seconds, without any mechanical mixing, by a purely chemico-physical process, into a milk-white emulsion, which, as may be seen under the microscope, consists of the very finest drops. But this takes place only when there exists a quite definite relation of solubility between the soaps formed by the combination of the alkalies present with the fatty acids and the surrounding menstruum, so that the disturbing precipitation of soap membranes is prevented. On account of its alkaline constituents, the bile is capable of forming soaps with the fatty acids; and, secondly, it keeps the soaps so formed in perfect solution. But it is too rich in alkalies to effect this without dilution or partial combination of its alkalies, and so under certain conditions it may act so as to prevent the formation of an emulsion. The conditions which are unfavourable to the formation of a good emulsion must be corrected by opposing them, and for this purpose there is abundant opportunity in the intestine. On the one hand, it is necessary to dissolve the little soluble soda and potash soaps, which are derived from the salt and lime of the food, while on the other a too high degree of acidity must be moderated, because both these conditions, as Gad has shown, diminish the goodness of the resulting emulsion. It is certain that the discharge of bile has an influence which, if not very definite, is still very marked. Bidder and Schmidt observed the proportion of the fat in the chyle of two dogs, of which one had a biliary fistula: it was as 32 : 2. Schwann, and after him others, maintained biliary fistulæ a long time without marked injury to life, but still only, as Voit pointed out, when the loss of absorbable material was compensated for by increased food.

Finally, bile possesses an anti-fermentative action, and as the older authors concluded, from observing the hard fæces of jaundiced patients, it is also a purgative. These proper-

ties, like many other observations of our acute and observant forefathers, have been fully confirmed by experiment. The bile acids, in fact, act by inducing increased peristalsis. But you see that all these processes do not consume the bile or modify it importantly, and the question now arises, what becomes of the elements of the bile when they have got into the intestine? A part, *e.g.* the cholesterine, a fraction of the bile acids and its pigment, indisputably leaves the body with the fæces. But Bidder and Schmidt found in the fæces of five days the constituents of only four grammes of bile, with 0.38 sulphur; whilst, according to an approximative estimate, about 39.5 grammes with 2.37 sulphur were passed into the intestine. Where is the remainder? The answer to this question, hitherto scarcely given at all or in contradictory senses, has been reached by means of an interesting series of experiments by Tappeiner. It concerns only the bile acids, which, as I shall premise, hitherto have not been found in the blood, although their presence, when in large quantities, is indicated by the slowing of the pulse. On the other hand, Tappeiner has found them in 150 ccm. of chyle from the thoracic duct, and Draggendorf in non-jaundiced urine. A part, at all events, also passes out of the intestine into the vessels, and it is in the jejunum and ileum that this absorption takes place. This Tappeiner has proved by the aid of an exact method of estimating the bile acids. He injected solutions of known concentration into ligatured portions of intestine, and after a certain time saw how much had been absorbed. This showed that the solution injected into the ligatured loop of duodenum remained unchanged, whilst in the similarly treated loops of jejunum and ileum absorption had taken place. But even in the jejunum all the bile acids were not taken up by the intestinal epithelium, but only the glycocholate of soda, and Tappeiner makes it probable that the different relations of the particular segments of gut depend upon a specific capacity of their epithelium for the absorption of bile acids.

Milk and bile injected at the same time into a loop of duodenum or jejunum behave very differently. The milk is absorbed and fills the vessels with milk-white chyle ; the bile, on the other hand, that is the taurocholate of sodium, remains in the intestine. This experiment, interesting in itself, gains from the latter fact a very special significance for the doctrines of absorption, as we shall see in the proper place.

But this is all we know concerning the function and persistence of the bile. Little enough, when we think of the dominating rôle which it at one time played in medicine. Moreover, we know almost nothing as to the pathological changes of the bile in diseases, or of the influence which changed bile exerts on the digestive processes. Such statements as Frerichs, that post mortem there have been found in the gall-bladder albumen in hyperæmia of the liver, and leucin and tyrosin in typhus, have no great significance. In general, changes of the liver parenchyma appear to effect no special change in the bile. I may pass over those changes which are found in closure of the bile-ducts, as well as the description of gall-stones, as not belonging to our subject.

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LECTURE IX.

Gentlemen,—If our knowledge of the pancreas had developed in proportion to the zeal which it has evoked from physiologists, it would be the best known gland in the body. Regnier de Graaf, as early as 1662, tied a canula in the pancreatic duct of a sheep to obtain the secretion, but, according to Frerichs, he appears to have been satisfied with the observation of certain superficial characters of the fluid obtained. After him, almost all great physiologists who have worked at the digestive processes, have included the pancreas in their round of investigations. Purkinje and Pappenheim, in 1836, found that the pancreas had a digestive power over albuminoids; but Bernard and Frerichs first succeeded in laying the proper foundation of our present knowledge concerning this gland.

The pancreas is formed on the type of the salivary glands, for the circumstance that the organ has a more extended surface and is not so roundly compressed into the smallest space, so that it has more elongated than rounded acini, makes merely a superficial difference. Therefore, as I may refer you to the description of the salivary glands, I can limit myself to some special points in the changes which the cells undergo during digestion. You may remember that we could distinguish in the cells of the acini of the salivary glands an inner clear mucous layer, and an outer zone with

granular protoplasm. The latter is coloured by carmine, and during the activity of the gland spreads itself over the entire cell. Exactly the reverse occurs in the pancreas. Here it is the outer zone of the cells, which lies against the membrana propria, that is homogeneous, clear, and colours with carmine; while the inner layer next the lumen is granular, dark, and not readily stained. The somewhat flattened nuclei lie at the junction of the two layers. During digestion the cells shrink as in the salivary glands, but the granular inner zone disappears gradually, and the clear outer zone extends over the whole acinus, the nuclei becoming round and large. With the aid of a special apparatus, Kühne and Lea watched by the microscope the delicate rabbit's pancreas in the living animal during digestion; they saw that some tubules were smooth-bordered, others were notched, the latter change being due to the activity of the particular acinus. These investigators could confirm the disappearance of the granular layer, which is described as Bernard's granular layer, as we have stated, following Heidenhain, and we may say with the latter: "During their physiological activity a very extensive exchange takes place in the cells; consumption of matter inside, preparation of matter outside; the inner converting the granules into the secreting elements, the outer employing the nutritive materials to form a homogeneous substance, which on its side, later on, is transformed into granular masses." I can confirm these statements, at least for the two extreme conditions of fasting and digesting animals, although I have not found the distinction between active and passive glands so striking as, for instance, in the stomach. Meanwhile, I will not omit, in reference to the previously discussed question (see p. 27) as to the new formation of cells during the activity of the gland, to draw your attention to the fact that neither Kühne nor Heidenhain, the newest and most trustworthy investigators in this region, speak of a new formation of gland cells during digestion. It is probable that the secretion out of the cells takes place

only on the side of cells next to the lumen of the duct. At least Kühne made the interesting observation that blood corpuscles which get between the cells and the membrana propria when a dilute solution of blood is injected under high pressure into the duct, are not dissolved, whilst they soon disappear in the larger passages. The pancreas is entirely dependent in its function upon the circulation. The gland of a fasting dog is flabby, whitish or yellowish; while during digestion it swells and has a beautiful rosy colour. Here, too, during the activity of the gland, the venous blood runs out of a bright arterial red colour, and, according to Kühne, there occurs a capillary and venous pulse, with dilatation of the capillaries. What nerves serve as bearers of these digestive influences is meanwhile only incompletely made out, and there is scarcely anything known of their connections with the secreting cells. Bernstein found that centripetal stimulation of the vagus stopped secretion, a fact which harmonises with the discoveries of Weinmann and Bernard that during vomiting the pancreatic secretion stops, whilst peripheral stimulation of the vagus or section of it remains without any effect. If this is so, we should expect to find a system of independent ganglia, such as Goltz describes in the stomach; and as smooth muscular fibres have been as a rule only sparingly seen, the increase of secretion obtained by Kühne by direct faradisation of the gland, is probably to be attributed to the stimulus of such ganglia. These things, however, are very difficult to decide, because we are not in a position to observe all the conditions of the pancreatic secretion; and, besides, the gland itself appears to be exceptionally sensitive, and rapidly gives evidence of the slightest irritation by changes in its secretion. On these grounds also, I abstain from giving you detailed statements as to the quantity of the secretion or its percentage composition. I have obtained at the same period of digestion in about equally large dogs, fed at the same time, sometimes copious, sometimes quite scanty secretion,

without being able to assign any cause for this difference. Still the absolute amount is never very great. Bernstein found in the dog 2—15 ccm. in an hour, but I have never obtained more than at most 5—6 ccm. in the same time. Frerichs, however, could collect 25 ccm. in three quarters of an hour from an ass. The secreted fluid is, in my experience, always clear, rather thick, free from colour or smell, and of an alkaline reaction, only clouded at first by the products of the irritation of the duct. The quantity of the solid constituents varies from 3—10 p.c., which includes the ordinary inorganic salts, albuminoids and the specific ferments of the juice, which stamp it as an entirely special secretion. Of these, the pancreatic juice does not include one, but three, which certainly have not yet been obtained pure, but are recognisable from their actions with the greatest distinctness. They are (1) diastatic, (2) albumen-dissolving, and (3) fat-splitting ferments. Just as in the case of pepsin, the pancreatic ferments, which collectively are called pancreatin, may be extracted from the gland by infusion with water, glycerine, salicylic acid, bicarbonate of soda, &c. The albumen-dissolving and diastatic ferments are most readily obtained; the fat-splitting ferment is more difficult to prepare, and seems to be easily decomposed. By precipitation with alcohol and drying the precipitate, we obtain the ferments in the form of a white amorphous powder.

Concerning the diastatic ferment, which was already known to Valentin and Frerichs, we know only that it is equalled, not to say excelled, in activity by no other ferment. The smallest amount of fresh pancreatic juice at the body temperature changes starch paste almost immediately into grape sugar. Cane sugar, and a nearly related hydrocarbon, inulin, do not become changed, as I can confirm for the former. Zweifel and Korrwin failed to find the ferment in the pancreas of newly-born children, but I have been able to obtain a perfectly active extract from the pancreas of a puppy three days old. The action of the pancreatic juice on albumens

takes place freely only in alkaline or neutral solutions, slowly and laboriously in feebly acid fluids. Consequently, the albumen does not swell as in acid gastric juice, and become converted into syntonin, but shrinks and remains a longer time coherent, and dissolves after having been previously converted into another modification, globulin, insoluble in water. The final soluble modification is a body resembling pepsin-peptone in all its reactions. This "pancreas-peptone" is not coagulated by heat. No precipitate is obtained from its solutions when treated with glacial acetic acid and ferrocyanide of potassium, or with tannin, iodide of mercury and potassium, picric acid, &c.

Kühne has prepared from the pancreatic tissues, by the aid of a very complicated method, a body which he regards as the pure ferment and calls "trypsin." But its purity is otherwise doubtful, and especially because this "trypsin," according to its reactions as given by Kühne, must be mixed in no small degree with albumen or some nearly related body.

According to this investigator, the digestion of albumen by trypsin passes through two stages; in the first, the albumen is converted into peptone; in the second, one half of the peptone, which he terms "hemipeptone," is further decomposed in a similar way, while the other remains as "antipeptone," which undergoes no further change. Re-investigation of these statements is needed to establish their correctness; but so much is certain, that the pancreatic digestion is not concluded with the formation of peptones. If we mix an albuminate, or, best of all, fibrine, with pancreatic juice or gland extract at the body temperature, in salicylic acid solution—which acid, as Kühne has shown, does not specially injure the action of trypsin—we find other bodies after a longer or shorter time, according to the activity of the extract employed, together with the peptones. These one would at first ascribe to putrefaction of the albumen, but the digesting mixture shows nowhere any trace of putrefac-

tion by smell or contents (bacteria, vibriones). These bodies are leucin, tyrosin, hypoxanthin, and asparaginic acid. On the other hand, if we have employed a feebly alkaline or neutral solution, we soon find a faint putrefactive odour, with development of bacteria and other signs of putrefaction, and, in addition to the above-named substances, the further products of the putrefaction of albumen, ammonia, sulphuretted hydrogen, hydrogen and carbonic acid. It is not easy to decide clearly in this case when putrefaction begins and the normal digestion ceases, unless we can employ, as Hüfner has done, quite special precautions and preservatives against the entrance of putrefactive organisms. But he obtained, while excluding all putrefactive ferments, peptone, leucin and tyrosin—he did not look for hypoxanthin, asparaginic acid and further products—as the result of the normal physiological pancreatic digestion, to which, according to other authors, hypoxanthin and asparaginic acid may be added. Hüfner also succeeded by another means in proving the same bodies to be products of the physiological pancreatic digestion, and therefore the remarkable fact is made certain, that those bodies which we meet with in ordinary putrefaction of albumen, and which we may derive by chemical agents from fresh albumen, are formed by the normal action of "trypsin."

Nencki has performed similar experiments with gelatine to those of Hüfner with albumen, and has proved the formation of gelatine-peptone, which in its reactions scarcely differs from albumen-peptone, as well as the formation of glycocoll, gelatine-sugar, a body formed in the decomposition of gelatine by sulphuric acid. The pancreatic digestion in the intestine, as in the retort of the chemist, does not remain stationary at the "normal digestive products," but tends more or less to form the said putrefactive products which we shall repeatedly meet with in the description of the digestion in the small and large intestine. If I were to give you a table of the action of the pancreas on albumen and gelatine,

similar to that for pepsin, leaving out chemical details and accepting Kühne's views, it would take the following shape:

Albumen + Trypsin (Pancreatin) + Soda Solution of 1 p.c. forms at the body temperature first Globulin insoluble in water, and then

Hemipeptone		Antipeptone
Normal Digestive Products		Putrefactive Products
Leucin	Indol	
Tyrosin	Phenol	
Hypoxanthin	Fatty Acids	
Asparaginic Acid	Ammonia	
Glycocoll	Sulphuretted Hydrogen	
	Hydrogen	
	Carbonic Acid	

It scarcely needs to be mentioned that the occurrence of the bodies described as products of putrefaction is contemporaneous with the development of bacteria and micrococci, and as an almost universally admitted result of them. These organisms are taken up with the food, and find in the intestine a favourable nidus for their development. It is certain they are not pre-formed in the tissues, as some maintain, but when they are found, as by Nencki, in fresh pancreas, they have got in by chance from the intestine. I have often examined the fresh pancreas of dogs and rabbits just killed, and have never found bacteria or micrococci. The experiments of Hüfner, already referred to, show, moreover, that these bodies have absolutely nothing to do with the products of pure pancreatic digestion, so far at least as concerns the formation of leucin and tyrosin.

There is a remarkable observation of Liversedge, that a pancreas completely exhausted by glycerine, after exposure for some time to the air, again yields an active diastatic glycerine extract. He concludes, "that there is in the pancreas a substance inactive in itself, but which is converted by a process of decomposition into a ferment," just as the glycogen of the liver, after the death of the animal, is converted into sugar. Heidenhain found further that the glycerine extract of fresh pancreas contained only a trace of

the albumen-digesting ferment, but, on the contrary, a body which in a watery infusion of the gland or by simple exposure to the air changed into the active ferment. He called it "zymogen," after analogy with glycogen, that is, the preceding stage of the ferment, and he proved that it was changed into the specific ferment most easily in warm and acid watery solutions, much slower in neutral or alkaline solutions. These highly interesting observations, which harmonise with the similar results in the liver and parotid, permit the conclusion that the active ferment develops just at the moment of secretion, perhaps under the influence of a similar formation of acid such as is produced in muscle by its activity, and, according to Podolinsky's experiments, we may believe it is formed by the action of the oxygen of the blood. It unites with the other definite contents of the gland the products of fermentative putrefaction, namely, leucin, tyrosin and hypoxanthin, of which the former were prepared by Frerichs and Staedeler, the latter by Salomon. The third, *the fat-splitting ferment*, has not yet been isolated, and is only recognisable in the action of the original juice or in an extract of intestine. It is best demonstrated with quite fresh juice and a neutral fat which has been treated with a few drops of alkaline slightly violet coloured alcoholic solution of aniline purple. If we warm the whole some time in a water-bath, the violet fat and alcohol solution becomes yellow by the formation of fatty acids. Glycerine and a fatty acid are formed according to the following formula, for which I take the ordinary fat, our tallow:

$$\begin{array}{llll} \text{Tristearine} + \text{Ferment} & + \text{Water} & = \text{Glycerine} & + \text{Stearic Acid.} \\ C_{57}\,H_{110}\,O_3 & + 3\,(H_2\,O) & = C_3\,H_8\,O_3 & + C_{54}\,H_{108}\,O_6 \end{array}$$

On the significance of this formation of fatty acids I have already had the opportunity of remarking when speaking of the action of bile. Their formation takes place slower than sugar and probably of peptone.

You see from all this, Gentlemen, that our knowledge of the nature of the pancreas and its juice is not so insignifi-

cant, and we are quite in a position to analyse its action. Would it were so with its pathology! But on this point we can only advance vague notions, if we no longer, like Vesal, regard the pancreas as the cushion for the full stomach, or, like Riolan, Sylvius and Hoffmann, as the cause of hypochondriasis, ague and other fevers. We know besides some morbid changes in the gland. Thus we know that the occlusion of the pancreatic duct, which generally occurs from tumours in the head of the pancreas, rarely from parasites or foreign bodies, may lead to dilatation of the duct, to cyst formation, called, by Virchow, ranula pancreatica, and to atrophy of the gland substance, as Pawlow has recently produced by experimental ligature of the duct. A more or less extensive part of the gland substance may become destroyed, chiefly by cancerous new formations or by fatty degeneration, and hæmorrhages result in the substance of the gland, with sudden or gradual death to the individual. Inflammations, abscesses, &c., occur in the gland, but we know actually nothing of the effect of these on digestion or metabolism. As the first consequence of the abolished function of the pancreas, we notice failure to absorb fats. In fact, Brunner saw the intestinal contents dry up and become fatty after extirpation of the pancreas, and Bright noticed, in 1832, a peculiar fatty character of the fæces which occurred in a case of degeneration of the pancreas and ulceration of the duodenum. Similar observations were, later on, again described and attributed to the failure of pancreatic juice. But it is quite certain that cases are to be observed of degeneration of the pancreas or closure of its duct without fatty alvine evacuations. I myself have published two such cases in a dissertation by Sauter, in which the ductus choledochus was closed by a tumour, and the flow of bile into the intestine was also prevented. Moreover, this increase of fat in the stools is by no means a necessary attribute of pancreatic diseases, nor has it when present any certain diagnostic value, because the same phenomenon, according

to English authors, occurs in ulceration of the duodenum. Similarly, glycosuria occurs in pancreatic diseases, which in recent times has found its chief champion in Catani. But it was Bright who first described this relation; and Frerichs, at the time he wrote his Clinical History of Liver Diseases, had observed, out of nine cases of diabetes, atrophy or fatty degeneration of the pancreas five times. Catani has found in four out of five observations undoubted fatty degeneration and atrophy of the gland, and similar statements have been made by other observers.

We must admit that the pancreas has certain connections with diabetes. Some regard the disease of the pancreas as the cause, some as the result. This connection is supported by the relation between the pancreas and the cœliac plexus, especially by an observation of Klebs of atrophy of the pancreas associated with degeneration of a certain number of the ganglion cells of the cœliac plexus. But on this point we have not arrived at any certain knowledge. I have seen more cases of diabetes without atrophy of the pancreas than with it.

In diseases of the pancreas, an extraordinarily rapid wasting has been noticed. Here a causal connection may very well exist, although Colin's animals bore extirpation of the pancreas without injury, and Schiff saw artificially induced atrophy of the gland remain without visible results. Meanwhile, with respect to these and all similar experiments, we may urge that they extended over too short a time, and that chronic destruction acts very differently to acute softening. Genuine simple pancreatic degeneration is one of the rarest occurrences. There nearly always are present metastases to the organs adjacent to the gland, which make the connections illusive between these general diseases and the pancreas. Schiff maintains, finally, that the pancreas is definitely and intimately dependent upon the spleen. After extirpation or elimination of the latter, the secretion of active pancreatic juice stops. This view, as I have proved,

originates in a complete mistake. Dogs, whose spleens have been extirpated, secrete as before a perfectly efficient secretion.

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LECTURE X.

Gentlemen,—With the pancreatic digestion the digestive function of the alimentary canal reaches its highest point. What happens in the long course through the small and large intestine is chiefly directed to the absorption of altered nutriment and the elimination of unused refuse. Numerous glands, it is true, exist in the wall of the intestine, the latest and completest description of which we owe to Schwalbe, but it is not ascertained what and how great a part Brunner's and Lieberkühn's glands, the solitary follicles and Peyer's patches, play in the digestive processes. It is in the nature of things that we cannot investigate the particular secretion of each gland, but only a mixture of them, the intestinal juice or an infusion of more or less carefully isolated Brunner's glands. I will give you only a few hints concerning the histological structure of these organs.

Brunner's glands are tubular much convoluted glands lying in the submucous tissue, and most numerous near the pylorus. They possess membraneless cells with granular contents and elliptical nuclei imbedded in a homogeneous basis substance. In respect to their membrana propria, ducts, blood and lymph vessels, they bear such a close resemblance to the acinous glands, that we may regard them as a mixed type between tubular and acinous glands, but still, as was first pointed out by Schwalbe and confirmed by

Grützner, they possess the greatest resemblance to the pyloric glands in the stomach. During digestion the cells are large and clear, while fasting small and cloudy, so that the same peculiar change in the cell dependent upon its functions occurs in them which we have so repeatedly met with.

Lieberkühn's glands are also tubular, with membraneless cells having granular contents and a homogeneous basis substance, inclosed in a membrana propria of connective tissue. According to Schwalbe, they differ in some minute details from Brunner's glands concerning the course of the tubes and the shape of their cells. In these, the proper secreting cells pass up from the fundus close to the lumen of the gland, and are easily distinguished from the epithelium of the intestine by the absence of the so-called cover.

The solitary glands and Peyer's patches are not a secreting but an absorbing apparatus, which have many analogies with the follicles of the tonsils, the thymus, or the malpighian bodies of the spleen. They are spherical, lie close under the mucous surface, have a capsule of connective tissue in which numerous round cells and nuclei are imbedded in a generally turbid fluid coagulable by acetic acid, and surrounded by a capillary network sending branches into the follicle. They are, as you know, most frequently found in the neighbourhood of the ileo-cæcal valve.

Brunner's glands lie so close together in the upper part of the small intestine, that we may regard an infusion of this portion as an extract of them, without fear of its containing much foreign admixture. Such an extract, prepared, according to Grützner, with glycerine or 0.1 p.c. solution of hydrochloric acid, dissolves fibrine readily, and, according to Budge and Krolow, has also a diastatic action, which makes the former investigator dispute the complete analogy between Brunner's glands and the pyloric gastric glands. I have obtained only one active extract, so that my experience agrees with that of Grützner. As to the connection of the nerves with these glands, and their anatomical and physio-

logical relations, we know very little more than can be learned from this experiment of Moreau's: he placed four ligatures at equal distances upon a piece of intestine, cut all the nerves which went to the middle of these three compartments, and replaced the whole in the abdominal cavity; after a certain time he found the upper and lower loops empty as before, but the middle loop was filled with much fluid—100 grms. in three hours—containing albumen and inorganic salts. This experiment hardly touches the question of the innervation of the glands; it is much more important for the question of diarrhœa. M. Moreau neglected to perform any experiment on the digestive properties of the excreted fluid, although it was quite easy to do so; it is therefore doubtful whether it was simply a transudation from the blood resulting from the paralysis of the vessels, or a secretion of the intestinal glands. I do not know that his experiments have been repeated by others for this purpose.

This is the place to introduce some account of the movements of the intestine in their dependence upon the nervous system. An easily accounted-for uncertainty reigns over this region, the elucidation of which would be of great and practical interest. The study of the intestinal movements in their normal relations is rendered difficult by the deep invasion of the body necessitated in experiments upon them. We do not know for certain how to decide how much of the phenomena observed may be due to the lesion, as the result of accidental but unavoidable injuries. It is now known that every local irritation of an exposed intestine has for its consequence a usually short local wave of contraction or peristaltic movement, which has been explained, when ganglionic plexuses are present in the walls (Auerbach's plexus mesentericus), as a reflex irritation coming from the ganglion cells. The activity of these plexuses can give rise to spontaneous intestinal movements. But it is not quite clearly shown *where* we can produce local contractions. We must either assume the presence of ganglia, as we have done above with reference

to Goltz's experiment on the gastric innervation, or, like Engelmann, take refuge in another hypothesis which cannot be detailed here. But the broader, longer waves are obviously to be ascribed to the general causes lying outside the organ. They can be attributed either directly to the terminal nervous apparatus in the intestine, or indirectly to the changes in its circulation. It was formerly believed that the movements of the intestine were caused by vascular anæmia, by obstruction of the aorta (Schiff), or general changes in the circulation in the intestinal vessels (Donders), while hyperæmia checked the movements (Betz). But this is not altogether correct. Pflüger showed by his famous discovery of the inhibitory power of the splanchnics on the intestinal movements, that, on the contrary, vascular anæmia may be combined with inhibition, and hyperæmia with excitation of the peristalsis. Mayer and Basch saw compression of the aorta followed by quieter movement or by stasis of the movements of the intestine. But the constancy of the splanchnic influence cannot be altogether confirmed. It is the same with stimulation of the vagus or artificial hindrance to the respiration, two factors which equally should have peristalsis as a constant result. All these give irregular results, sometimes positive, sometimes negative, sometimes none at all. Finally, Braam Houckgeest has endeavoured to get rid of the irritating influence of the atmospheric air in the examination of the exposed intestine, by opening and observing the abdominal cavity of animals under water (½ p.c. solution of common salt). He confirms Pflüger's statements concerning the splanchnic. Paralysis (*i.e.* section) of this nerve, which, as you know, is accompanied with hyperæmia of the intestinal vessels, is followed by increased peristalsis, that is, increased activity of the motor elements of the small intestine; while stimulation of the splanchnic, which causes vascular contraction and anæmia, is followed by inhibition of the movements. The vagus, however, influences peristalsis only indirectly, by causing contraction of the stomach, and thereby gives an

impulse to the intestinal movements, whilst peristaltic waves may be induced in any part of the intestine without the intervention of the vagus. Finally, the circulation is so far important as the "pouring out of digestive juices" in any part of the intestine causes spontaneous movements, while anæmia of the intestine always stops or at least enfeebles them. Antiperistaltic movements never occur in normal living animals. Moreover, Horvath's statement is of practical interest, that cold from 0° to 19° causes a prolonged or complete cessation of peristalsis, a fact of which I have made use for some time in the treatment of the diarrhœa of children, by injecting cold water into the intestine.

The intestinal juice is best obtained by means of Thiry's fistulæ. An excised piece of intestine still left in connection with the mesentery is sewn up at one end, while the other is united to the abdominal wound. The continuity of the intestine is repaired by carefully sewing the ends together. The secretion of these fistulæ is regarded as normal intestinal juice, but it may be questioned how far the secretion of such an intestinal pocket exhibits the normal relations, and the following data, upon which there is by no means a desirable harmony, are to be accepted with a certain amount of reserve. This uncertainty is explicable, if we consider how easily after such an operation vascular alterations may occur, quite apart from the irritation to the mucous membrane, which may lead to transudations from the blood, and quantitative or qualitative changes in the fluid from the fistula. Every one knows who has worked at the intestine and mesentery how extraordinarily irritable the vessels are, and the experiment of Moreau just related is so far evidence of this. Therefore the fistula does not secrete spontaneously, but only upon mechanical irritation. Neither direct irritation of the vagus nor reflex irritation, as by rubbing the abdomen with croton oil, gives rise to secretion. Thiry found the secretion alkaline, opalescent, clear sherry-coloured, sp. gr. 10.11, and estimated that a dog in from

two to seven hours after feeding secreted in his whole intestine about 350 grms. The secretion contains albumen, and has about 2.4 p.c. of solids, of which 1.53 p.c. are organic. As to its action, agreement prevails only on one point, namely, that it dissolves albumen. With respect to the rest, the statements diverge widely, some asserting it to have a fermentative action on other albuminoids or on starch, while others deny these. A very recent observation of Demant's was made on the secretion of a fistula of the ileum, in a patient whose upper intestinal contents were separated from it and emptied by a second fistula; he obtained only a diastatic and inverting ferment in the intestinal juice, but found neither peptonising nor fat-splitting properties in it. This might to a certain extent decide the question, but for the objection that the activity of the secreting apparatus of the lower intestine—the patient had had no stool for months—may have been enfeebled or altered by the long disuse. I quite agree with the views of Hoppe-Seyler on the value of the above statements respecting the intestinal juice, and therefore omit further details, so as not to complicate the discussion. As in the large intestine either none or only traces of a digestive fluid are secreted, and the absorbing function of the intestine becomes almost its exclusive business, we can, so soon as we have considered the constitution of the intestinal contents, in so far as they are still preserved, approach the most important and prominent peculiarity of the intestinal mucous membrane, its absorbing function.

The chyme, the composition of which we have described at its entrance into the intestine, becomes altered as it passes down the intestine in its chemical and physical relations in the following manner: the reaction becomes alkaline or at least neutral in the jejunum, as in my case before alluded to. In the ileum it becomes acid from the formation of acids from the putrefaction of albumen and fermentative processes. The substances which we have already learnt to recognise

as the products of putrefaction, are in fact all, or nearly all, present in the lower part of the alimentary canal, and owe their existence obviously to the same putrefactive processes as produce them outside the animal body, only that, favoured here by the natural conditions, they proceed more actively than elsewhere, and are accompanied by fermentative processes which lead to the formation of lactic acid, butyric acid, &c. I have only to refer you to the formulæ which I showed you previously (p. 22), for these processes, for you to have at one glance the whole of these bodies before your eyes. If you recal at the same time the obscure proposition of the iatro-chemical school related in the introductory Lecture, which made the digestion a putrefactive process, these remarkable facts acquire in themselves an increased interest, and we are reminded of an apt remark of du Bois Reymond's that the curve of scientific opinion always comes back after a certain time to its starting-point.

There are particularly two of these bodies which have excited in recent times an overwhelming amount of attention; these are indol and phenol. Both appear in the urine, the first as indican, which is an oxidation product of indol; the other, according to Baumann, in a form combined with sulphuric acid, sulpho-carbolic acid or its salts. Both are dependent for their occurrence and their quantity upon the intensity of the putrefaction going on in the intestine and the rapidity of the movements of the intestinal contents or their stay in the lower portion of the canal. But they have, like all the bodies belonging to this group, scarcely anything to do with the true digestive and nutritive processes. In cases like that of mine, the lower part of the ileum and the large intestine were as good as completely closed, and the entire intestinal contents down to the fistula, which was probably seated in the lower third of the ileum, were discharged by it and were completely absent lower down, only returning when the connection between the upper and lower intestine was renewed by operation.

Still the nutrition of the patient proceeded well, and, considering the general derangement, was particularly good. Indol and phenol are allied products, which the body gets rid of as waste through two channels, the kidneys and the intestine. The hopes have not been confirmed which were first raised by Jaffé's experiments, that close connections might be formed between pathological conditions of the intestine and the excretion of these bodies. Senator, whom I can completely confirm from my own experience, has drawn attention to the inconstancy in the amount of indican excreted. The same, according to Brieger, is true of phenol, and when we consider how many factors participate in the excretion of these substances—food, rapidity of peristalsis, intensity of putrefaction, amount of absorption—we cannot be surprised at this.

But, if we turn away from this practical point, it is certainly very interesting that phenol, which we make use of extensively every day for its antiseptic properties, should be found as a product of putrefaction, and that actually in our own intestines!

The intestinal gases, the formation of which is explained by the table of fermentations, consist of carbonic acid, hydrogen, nitrogen, sulphuretted hydrogen, and marsh gas, which last is formed by a special fermentation, marsh gas fermentation, the substratum of which exists in the cellulose taken in with vegetable food. These amounts vary very much, being in part dependent upon the diet. I may remind you of the flatulence following ingestion of certainly easily fermentable vegetables, cabbages, &c. In excessive meteorism, such as is caused by paralysis of the intestines, *e.g.* in typhus, we find scarcely any carbonic acid and principally nitrogen; an analysis of the gas obtained by puncture in such a case gave me 8.3 p.c. of CO_2, and the remainder nitrogen, mixed with some oxygen derived from the atmosphere, which entered during the experiment. In a woman aged 54, with a stricture of the rectum, which could be opened only with the help of a

bougie, and ordinarily caused fæcal retention and colossal meteorism, I emptied the gas collected in the intestine by means of a stomach tube, and found, seven hours after food (soup and bread), 6.9 p.c. CO_2, 11.64 p.c. H, 81.03 p.c. N. Ruge found as much as 50 p.c. of marsh gas in human flatus after eating vegetables.

The more the contents of the intestine pass downwards, the more do they become exhausted and inspissated. For this the rapidity of the peristalsis is the decisive factor. At the same time we must not imagine that such matters only are excreted with the fæces as are no longer useful to the organism. A part of the nutrient matter leaves the body under ordinary circumstances in this way, frequently only slightly changed. This is the surplus of the food which man, "the gluttonous animal," has taken in addition to his needs, and which passes too rapidly through the digestive tract to undergo the action of its secretions. The amount of this is naturally dependent upon individual conditions. In the stools of sucking infants, according to Wegscheider, we find coagulated milk, fat, peptones, and even an active diastatic ferment. In adults there are unaltered or only little changed remains of food. In addition there are mucus, epithelium, horny substances, pigments, fatty acids and products of putrefaction of albumen. Special interest is excited by a substance isolated by Brieger, Scatol, a final product of the putrefaction of albumen, which obviously causes the odour of fæces.

It is known that defæcation is subject, under normal conditions, to moderate variations in frequency and character. There are people who have two stools daily, others who have one every two or three days, and there have been cases recorded in which the bowels were opened regularly only once in eight or even fourteen days, the general health being quite good. Bristowe gives the maximum at from six to eight weeks. But the actions of drugs can defer the termination still longer; thus Williams records the case of a lady who,

in consequence of the habitual use of opium, had very frequently only one stool in six weeks, and once during a whole year had her bowels opened only four times. The reverse of this is found in the numerous stools of diarrhœa; indeed in dysentery they may reach thirty or forty in twenty-four hours. Their characters depend upon the secretion of the intestinal mucous membrane, the transudation from the blood, peristalsis and the particular kind of pathological process affecting the intestinal mucous membrane, and last, not least, the special contents of the intestine represented by the ingesta. Sometimes one, sometimes the other of these factors preponderates, and so it happens that the stools undergo great variations, not only in relation to their composition, but to their diagnostic value and pathological significance. Take, for example, the products of an ordinary summer diarrhœa and that occurring in albuminuria or consumption, which, regarded apart from the history, our knowledge does not in any way enable us to distinguish, yet which, in their pathological significance, are very widely distinct. A number of such instances might be given.

It is remarkable how few chemical analyses of diarrhœic stools we possess, if we except cholera and perhaps dysentery. The former is chiefly known from Schmidt's analysis, which I give here, and I place beside it the analysis of a stool produced by infusion of senna:

	Cholera.	Senna.
Water	984.15	969.75
Albumen		1.64
Organic matter . . .	5.15	20.03
Inorganic	8.19	8.58

If we desire to examine diarrhœic stools in practice, it is absolutely necessary not to confine ourselves to simple inspection, but to leave the stool to deposit its sediment in a tall glass. The odour may be reduced to a minimum in both solid and fluid stools, if, as I recommend, a thin layer of ether be poured over it. After settling, we can perceive

at a glance the approximate quantities of water and blood, the amount of mucus and solids, the colour of the sediment, and the supernatant fluid; we can recognise far better the quantity and the size of certain fibrinous exudations which, as you know, are found in the so-called diarrhœa tubularis, forming complete casts of the intestinal tube, and, finally, can easily select portions for microscopical examination. The contents—in pus and blood corpuscles, in abraded epithelium, mucus and elements of tumours—permit a conclusion, although only approximatively, as to the intensity and nature of the process going on in the intestine.

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Grützner. Notizen über einige ungeformte Fermente des Säugethier-Organismus. Pflüger's Archiv. Bd. vii. p. 285.

Krolow. Berliner klin. Wochenschrft. 1870, No. 1.

Moreau. Ueber die Folgen der Durchschneidung der Darmnerven. Cntrlbltt. f. d. Med. Wisschft. 1868, No. 14.

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Brieger. Ueber die flüchtige Bestandtheile der menschlichen Excremente. Journal f. pract. Chemie. Reprint. 1877; and Bericht. d. Berlin chem. Gesellschaft, 1877, p. 1027.

Bristowe. Obstruction of the Bowels. Reynold's System of Medicine, Vol. iii. p. 67. Williams' case is given here.

Schmidt. Characteristic der epidemischen Cholera gegenüber verwandten Transudations anomalien. Leipzig u. Mittau, 1850.

Thiry. Ueber eine Methode den Dünndarm zu isoliren. Wiener Sitzgsber. 1864, Bd. l. p. 77.

Jaffé. Ueber den Nachweis und die quantitative Bestimmung des Indicans im Harn. Pflüger's Archiv. Bd. iii. p. 448.

—— Ueber die Ausscheidung des Indicans unter physiolog. u. patholog. Verhaltnissen Virchow's Archiv. Bd. lxx.

Nencki. Ueber die Zersetzung der Gelatine und des Eiweisses bei der Fäulniss mit Pancreas. Festschrift. Bern. 1867.

Baumann. Ueber die Bildung von Phenol bei der Fäulniss von Eiweisskörpern. Berichte der Berl. chem. Geselschft. 1877, p. 685.

Baumann. Ueber gepaarte Schwefelsäuren im Organismus. Pflüger's Archiv. Bd. xiii. p. 285.

Senator. Ueber Indican und Kalk-Ausscheidung in Krankheiten. Cntrlbltt. f. d. med. Wissenschft. 1877, No. 20, 21.

Ruge. Beiträge zur Kenntniss der Darmgase. Wiener. Sitzgsber. math-naturw. Classe. Bd. lxiv. p. 740.

Zweifel. Untersuchungen über das Meconium. Archiv. f. Gynäcologie. Bd. vii. Heft. 3.

Demant. Ueber die Wirkung des menschlichen Darmsaftes. Virchow's Archiv. Bd. lxxvii. p. 419.

S. Mayer u. Basch. Untersuchungen über Darmbewegungen. Pflüger's Archiv. Bd. ii. p. 391.

v. Braam Houckgeest. Untersuchungen über Peristaltik des Magens und Darmcanals. Pflüger's Archiv. Bd. vi. p. 266, and Bd. viii. p. 163.

LECTURE XI.

Gentlemen,—We have to consider to-day *Absorption*, that is, the processes by which the contents of the intestine pass into the blood and chyle. There was a time, and that not so long ago, when it was believed absorption occurred only by the lacteals. That is not so. In the blood of the portal vein, between the intestine and the liver, we find sugar, a dextrine-like body, and peptone, which have passed direct from the intestine into the veins. The blood and chyle vessels participate in absorption, although apparently the latter perform the chief part, and especially that of taking up fat. Let us first see what is the structure of the apparatus of this absorption, the function of the villi, in connection with this interesting point. The villi are covered by a cylindrical, conical or pyramidal epithelium, the apices of which look towards the middle line of the villus, while their broad ends are turned towards the lumen of the intestine. The cells in the fasting state have finely granular turbid contents, and a large nucleus lying towards the apex. During digestion we can see in them numerous oil globules; indeed, Moleschott and Marfels maintain that they have seen in them (in the frog) choroidal pigment and blood corpuscles from other animals which were introduced into the intestine. The remarkable and exceptional character of this epithelium is the so-called "cover" (deckel), which is a small strip closing

the cell opposite the lumen of the intestine with fine longitudinal striæ, which, when looked at from above, have the appearance of numerous dots. This striation does not extend quite to the lower border, but ends a little higher, so that the " cover " has the appearance of a comb turned with its teeth upwards. Whether these striæ are pre-formed, or are post-mortem products of splitting of the cell contents—whether they represent a system of fine pores or canals which to a certain degree permit entrance to the proper cell cavity, or whether it is only an illusion produced by a kind of cilia possessed by these special cells—is a point upon which hitherto no agreement has been reached. The last view is defended with great determination by Thanhoffer: according to him, we have to do with moving protoplasmic cell processes, which by their motion introduce the smallest molecular particles, especially fat globules. In the middle of the villi, lying between the vein and artery, runs the lacteal, which passes into the sub-mucous tissue and then takes on the characters of a valved vein. The connection between this lacteal and the epithelium of the villi through a system of cells and their processes, which are either connective tissue cells or very similar to them, and stand in direct communication with the open apices of the epithelium, was previously demonstrated by Heidenhain, confirmed by Eimer and Tharschanoff, but denied by others. Although Heidenhain's observations were made on frogs, and analogous conditions in higher animals have not yet been shown to exist, there is much to be said in favour of admitting a direct communication between the central lacteal and the epithelium of the villus. Moreover, all authors agree that the intestinal contents have to pass on their way to the lacteal through very small capillary channels which are probably pre-formed; that, further, we meet with the intestinal contents (fat) in the epithelium during digestion; and that, finally, the cell contents, protoplasm and nucleus, undergo during this act no externally recognisable change. Brücke

has seen in the villi near the well-known longitudinal muscular fibres running from above downwards, circular, ring-like, smooth, muscular fibres, which by a sort of peristaltic contraction pump the contents of the villus towards the lacteal, and at the same time draw in new material, so that by the assistance of the valves already referred to the villus works like the heart.

The special process of absorption now appears as the proposition that the contents of the blood-vessels and lacteals and those of the intestine represent two fluids separated by a membrane, the wall of the villus, which behave as if in a dialyser, an explanation which at first sight offers no great difficulty. It is generally admitted that the exchange between the intestinal contents and the blood follows the laws of diffusion and endosmosis. This may be at once granted in so far as concerns the inorganic salts, but not for the other substances. The passage of water into the blood would be brought about by the previously mentioned high endosmotic equivalent of the albumen found in the blood, which favours a current of water out of the intestine into the richly albuminous blood; the absorption of peptones takes place in consequence of the great difference in the endosmotic equivalent between it and raw albumen, at least according to physical laws, and the like takes place for solutions of sugar. These views find experimental support in the experiments which have been made partly by Funke, partly by Becker and others, and which show that solutions of common salt, sugar and peptone, injected into ligatured loops of intestine, disappear from the loop in more or less time in proportion to their concentration. But it is plain that such experiments can teach us only the fact of absorption and the practical conditions respecting it, but not the details of the processes themselves. Still worse off are we with regard to fat. Fat does not diffuse at all, or at least not in a manner extensive enough for the purposes of absorption. A part of it, as we saw previously, becomes converted into soap and dissolved,

but a far larger part appears again as free fat in the chyle and blood, and may be seen in its resting-place between the intestine and the blood in the epithelium of the villi. Here we can only imagine a direct mechanical passage, which is rendered possible if the fat is finely divided (emulsified), so that it can pass through the epithelium or the pores of their covers. But such fine emulsions, as was formerly believed, are to be obtained outside the organism only by the employment of strong mechanical forces which cannot by any means be attained by the musculature of the intestine, and we were always in a dilemma how to explain the formation of the emulsion obviously present. You see now the significance of Gad's proof of the self-emulsification of fat (p. 83), which we have already spoken of in detail, especially as this investigator has made it probable that the fine fat-drops of the emulsion described do not surpass the diameter of an epithelial pore. The vexed question concerning the force which breaks up the fat in the intestine finds from this a satisfactory solution. They are the smallest and most imperceptible forces which in this instance, as so often in Nature, produce such great results.

The possibility of the passage of fat being demonstrated, the only question is, what force actually brings it about? All certain knowledge of this process is still wanting. In order to explain its absorption, we are in the habit of describing v. Wistinghausen's experiment, the outlines of which I can give you as follow:—Two almost capillary glass tubes, of which one is washed inside with a solution of bile acid, and the other with a solution of soda or water, are dipped side by side into a glass of oil. The oil rises in both by capillary attraction for some distance, but reaches about a millimetre higher in the tube containing bile acid than in the other. Further, bile acid favours the passage of fat through damp animal membranes; and as the epithelium of the villi in the intestine is bathed with bile, this circumstance greatly elucidates, if it does not solve, the

question of the passage of fat through the pores of the epithelium into the commencement of the lacteal. But such assistance would only be needed if the fat globules were too large to pass through the pores without resistance; otherwise they would be suspended in the stream of fluid which runs from the intestine to the lacteal, and they would be subject to the same laws of motion as this. But are the known physical laws sufficient to explain this motion, this passage? This cannot by any means be affirmed without reserve. Voit and Bauer have drawn attention to many facts which do not agree with simple diffusion or endosmosis. Only we should not need to fall back upon endosmosis and diffusion if we accept, with Brücke, a periodical contraction of the musculature of the villi, as before mentioned, a sort of pump action in the villi, which, *mutatis mutandis*, works like the heart; or if we accept the view that the mechanical force of the peristalsis drives the contents of the intestine into the blood and chyle vessels by a sort of filtration under pressure. But a pump ought to work regularly, and, without distinguishing between fluids of different composition, it should make the contents of the well (the intestine) come through the pipe (the cells and first lymph spaces) into the trough (the lacteal). But in the present case it is not so. We know that different substances in solution in the intestine do not pass into the chyle, and we have had this demonstrated by Tappeiner's experiments upon the variations in the absorption of bile acids in different portions of the intestine. Moreover, leucin and tyrosin have never been found in the repeatedly examined portal blood or chyle, although these bodies are formed by the pancreatic digestion, and at least the former is quite soluble in water. Simple pumping certainly does not take place, but the stimulated muscular action serves only as a means of motion for the stream once set in motion in the lacteals; and we may remember that the valves of the lacteals, beginning in the submucous coat, must promote this by preventing reflux. But this theory does not explain

the passage through the epithelium. The following suggestions of Hoppe-Seyler find their place here: 1, fat can pass undissolved into the chyle through the intestinal epithelium independently of the villi (in the lower animals); and 2, the absorption of water from the intestine into the blood is dependent upon healthy living epithelial cells, and simple irritation of these cells suffices to turn the stream from the blood and lymph into the intestine. Finally, Hoppe-Seyler adds, that a series of toxic substances, by killing or irritating the cylindrical epithelium, abolish or diminish absorption, as phosphorus, arsenic, preparations of antimony, jalap. The first and last of these points seem to me to be most important. The transudation of water into the intestine originates not in the irritation of the epithelium, but the vaso-motor nerves. We can completely kill the epithelium of a mucous membrane with nitrate of silver without causing a trace of œdema, which, however, occurs at once when substances which act more deeply are employed, and quite the same takes place on the external skin. In the second case also, the normal absorption from the intestine would be surpassed by the transudation out of the vessels, and therefore no conclusion would be possible from this condition as to a special function of the epithelium. But the above points are less easily rejected by the adherents to physical theory.

Ludwig has drawn attention through his pupil Zawilsky to the fact, that the quantity of fat present in the chyle is independent of the amount of water; whilst the view of a general filtration through the epithelium (whether endosmotic or mechanical by means of the muscles of the villi) would make a direct relation between fat and water very probable. If we were to ascribe the absorption to the laws of diffusion alone, when a dilute-solution of alcohol is injected into the intestine, water should pass out of the blood into the intestine, while just the reverse occurs. Thus Brieger found by experiments which he performed according to the method of Moreau (p. 100), that 0.5 p.c.—1 p.c. solutions of neutral

salts were followed by no transudation into the ligatured intestinal loops, but 20 p.c. solutions produced a clear yellow alkaline fluid, containing shreds of mucus, epithelium and mucous granules, so that irritation of the mucous membrane was a necessary stimulus to the process, which we are always accustomed to regard as simply due to the high endosmotic equivalent of the neutral salts. The objections thus multiply against the view that absorption is a purely physical phenomenon, and Hoppe-Seyler's description, although provisionally only an hypothesis, must receive the greatest consideration, "that absorption takes place mainly through chemical affinities, conditioned by the life of the cell, which is thereby itself changed and used up."

Where does absorption take place, and what is absorbed? The first is as easy as the second is difficult to answer. That the entire intestinal tract, from the stomach to the sphincter ani, participates in absorption in different degrees in different portions, has been placed beyond doubt by numerous observations and investigations. Principally, and in particular for fat, the small intestine, but the stomach and large intestine are also capable of transmitting nutriment into the vessels. The last, according to Voit and Bauer, absorbs least of all (of 12 grms. of goose fat injected, 2.2 grms. disappeared), and it first loses this power on account of its acid contents. Special interest attaches from a practical point of view to the question of absorption from the large intestine, which, thanks to Leube, plays in recent times a beneficent part in therapeutics by the use of nutrient enemata based thereupon. Leube has shown, as you know, that compounds of minced meat, fat, pancreas and water, injected per anum into an animal in a state of nitrogenous equilibrium, can maintain it in this condition for some time without any food being given it by the mouth, and he has applied this in practice with the happiest results. It is certainly impossible that a healthy person, much less a sick person, can be nourished for any length of time by the rectum, although each part of the intestinal

tract can act vicariously at times for others, because all the principal factors are, so to speak, in duplicate; yet the co-operation of all the factors is needed for the scantiest nutrition: without it no extensive absorption is possible. Voit and Bauer in their best case could only effect the absorption from the rectum of about a fourth part of the albumen necessary to life, with the addition of fat or hydrocarbons. The great value of nutritive enemata is not so much in prolonging the lives of patients with incurable strictures, carcinoma, &c., which make feeding impossible by the mouth, as in acute affections of the upper part of the digestive tract, by permitting its complete rest; and in this sense their employment is, to my mind, still much too little generalised amongst the profession. Finally, I must not omit that Savory maintains that there is a more rapid absorption of drugs from the intestine than from the stomach. The action of those administered by the mouth is weakened, partly from changes which the substances undergo from the gastric juice, partly from their dilution in the chyme.

The next question, *what* is absorbed? points chiefly to the bodies not arising from normal digestion, as we have learnt to recognise them, and the products of the complicating processes. Thus peptone, sugar, probably dextrine-like bodies, salts, water, gelatine, glycocoll, fat and soaps, perhaps also leucin, are directly taken up, as is proved by the presence of these substances in the blood and tissues. So, too, with some of the bodies ascribed to the putrefaction of albumen, indol and phenol, which we find again, although in an altered form, in the urine as indican and sulpho-carbolic acid. On the other hand, we know no positive facts which permit the view that undigested albumen on the one hand, or the remains of putrefactive products on the other, as well as a series of organic acids—acetic, butyric, carbonic, valerianic acids—partly introduced with the food, partly formed by fermentation of the hydrocarbons, do pass into the blood, or let us know the magnitude of this passage if it actually

occurs. We are just as little informed as to how far the gases, carbonic acid, hydrogen, marsh gas, sulphuretted hydrogen and ammonia, developed in these processes, find their way into the blood.

The question whether unchanged albumen coagulable by heat passes into the blood and becomes used up in nutrition, is sometimes affirmed, sometimes denied. Bernard and Pavy have proved that dissolved albumen, casein and globulin, injected into the blood, re-appear in the urine, and pass unchanged through the organism. It is known that after heavy meals a slight amount of albumen is occasionally present in the urine, a circumstance which appears to speak in favour of the passage of unchanged albumen into the blood. In fact, possibly a small part of undigested albumen may pass directly into the blood; but by far the greatest quantity of the albumen which forms our tissues and circulates in our blood, originates undoubtedly from peptone changed back again into albumen, which is effected, as shown already, by simple anhydration, a process which we find so often in the organism. The possibility of this is fully proved by the experiments of Maly, Plosz and Adamkiewicz, which agree in showing that feeding with pure peptone is sufficient for animal nutrition. We cannot see anything in the entire process of peptonisation, or in the transformation of sugar into starch, but a chemical contrivance which the organism employs in order to transport large masses of material in the shortest possible time and in the purest possible form. When this is effected, the animal body has at its command another means, anhydration, or the removal of water, to again consolidate the matter in question into its original form or one of its allied forms, and to store it up for use. Brücke, the most determined representative of the view that unchanged albumen is absorbed, has found ordinary unchanged albumen in the lacteals, and moreover shows that a completely dissolved digestive mixture of pepsin, albumen and hydrochloric acid, after neutralisation and removal of the precipitated

syntonin, gives, on heating, a precipitate of coagulable albumen, and argues, that if such solutions are absorbed, the coagulable albumen contained in them must be absorbed too. The first observation, made by such a careful observer, is, unless we have to do with some anomalous condition, of great weight. But the presence of coagulable albumen in apparently digested digestive mixtures, on which Brücke lays great stress, is due, as I have repeatedly proved, simply to incomplete digestion. If the digestion in such a solution be started anew by the addition of some new pepsin and hydrochloric acid, after a short time there is no longer any albumen present coagulable by heat. So much appears to be certain, by analogy with many other processes, that all digestive actions inside the organism proceed more quickly, and their products occur earlier, than we can imitate with our retorts and air-baths. We have, as we have said, no definite knowledge of the absorption of other substances. Probably they are taken up, but perhaps only in small quantities. For the gases, which must obey the laws of diffusion, it can be scarcely otherwise; and if we can trust the investigations of Casse, even sulphuretted hydrogen may pass directly into the blood without causing injury.

Naunyn, loc. cit., has found a dextrine-like body in the blood of the portal vein.

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Fortunatow. Ueber die Fettresorbtion und histologischen Structur der Dünndarmzotten. Pflüger's Archiv. Bd. xiv. p. 285.

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Becker. Ueber das Verhalten des Zuckers beim thierischen Stoffwechsel. Ztschrft. f. Wissenschftl. Zoologie, Bd. v. p. 123.

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Adamkiewicz. Loc. cit.

Plosz. Ueber Peptone und Ernährung mit denselben. Pflüger's Archiv. Bd. ix. p. 325, and Bd. x. p. 586.

Maly. Ueber die Chemische Zusammensetzung und physiol. Bedeutung. der Peptone. Pflüger's Archiv. Bd. ix. p. 585.

Pavy. Gulstonian Lectures on Assimilation, &c. The Lancet, 1863, p. 574.

Casse. De l'absorption de certains Gas dans l'economie animale et de leur élimination. Bruxelles, 1878.

Voit und Bauer. Ueber die Aufsaugung im Dick- und Dünndarm. Ztschrft. f. Biologie, Bd. v. p. 561.

LECTURE XII.

Gentlemen,—The intestinal tract forms a continuous canal from the beginning to the end, into which the various gland ducts open like tributaries, their specific secretions being not isolated, but complexly mingled in it. There exist also obviously certain reflex connections between the various organs. Richet saw in his patient with gastric fistula and stricture of the œsophagus, that when food was introduced into the stomach by a tube the salivary secretion was increased, and on chewing sapid and odorous substances a proportionally strong flow of gastric juice occurred. Moreover, according to the investigations of Hüfner, Munk and Kühne, the various secreting organs possess not only the main specific properties described in the previous chapters, such as in the saliva the action of ptyalin, in the gastric juice that of pepsin, but it may be easily proved that the actions of one gland approach in some degree to those of the others. Thus J. Munk found that saliva treated with hydrochloric acid digested fibrin and formed peptone; and, on the other hand, that a diastatic ferment could be separated by glycerine from the stomach and intestinal mucous membrane. Kühne records the same, but he also proves that trypsin is found only in the pancreas or its secretion. These are, however, accidental or at most concomitant phenomena of each special gland function, and indeed we can obtain similar slight

ferment actions, not only with the glands κατ' ἐξοχεν, but with many other tissues, such as the lungs and the blood.

Does one secretion prevent the action of another? The saliva is swallowed in great quantity, and must, as often stated, be rendered inactive by the acid gastric juice; and, conversely, by its alkalinity it may neutralise or alkalinise the reaction of the gastric juice, so as to stop the pepsin digestion. The latter is possible, but must be very rare, and only in the presence of excessive sialorrhœa, and is more imagined in theory than observed in practice. At least I know of no such cases either in literature or my own practice. The former is, as Frerichs showed, incorrect. Two per cent. solutions of starch mixed with human saliva, and rendered quite acid by hydrochloric acid, become changed into sugar. Besides, erythrodextrin is formed, recognisable by its red coloration with iodine solution, and under the microscope very few starch granules are to be found. On the other hand, bile, when it occurs in the stomach under pathological conditions, as we proved by experiment, stops the gastric digestion by forming, according to Burkart, a precipitate which mechanically throws down the pepsin. But at the same time you saw that a relatively large quantity was required to effect this, whilst smaller quantities had no influence on the gastric digestion, so that under ordinary conditions, in which only a small reflux of bile occurs, there can be no interference with the gastric digestion.

In the duodenum the pepsin digestion proceeds so long as the reaction is still acid; but as soon as it meets the bile, the syntonin and peptones are precipitated, the swollen albuminoids shrink up, and the pepsin is carried down mechanically with the precipitate. Then, with the assistance of large quantities of bile and pancreatic juice, the precipitated albumen becomes re-dissolved, and the digestive process re-commences. But this description has the fault of being too theoretical, as if things inside the intestine passed through the various phases and distinct stages that we see

and learn from our artificial digestion experiments. When we remember that the distance from the pylorus to the opening of the d. choledochus is uncommonly short (about 8 cm.), and that there the bile duct and pancreatic duct open immediately together, and that whilst by the action of the bile the foregoing reactions are proceeding, the pancreatic juice is at the same time present to reverse them, the process cannot be split up into distinct phases, but the actions of the bile and pancreatic juice must be understood to be bound up together most intimately. If we allow alcohol and sulphuric acid to act upon each other, ether is formed; but between the two, ethyl-sulphuric acid occurs, which we do not notice, because it is immediately transformed. Similarly there are no externally noticeable effects of the bile, because its products at once undergo further chemical changes, that is, are subjected to the pancreatic action.

In the subsequent divisions of the intestine, the bile and pancreatic juice co-operate in the digestion of fat, as we have detailed above. Finally, in how far putrefaction in the lower part of the intestine affects the normal pancreatic digestion, and whether both processes run on synchronously, or precede or follow one another, is uncertain. But we do not eat albumen, starch, that is hydrocarbon, and fat, or the different organic and inorganic acids and salts, in a pure condition, but take these things in our food in the most complicated and variously compounded shapes. Let us follow some of the most ordinary food on its way through the digestive tract, and see how far, how quickly, and when it is absorbed. This will be scarcely more than a retrospect over the path we have been treading, and the employment of the knowledge we have gained about articles of food, points which, strictly speaking, are included under dietetics. Still we shall not examine the various foods in their composition, digestibility, metabolic importance and so on, but review various groups in respect to the relations of their nutrient parts to digestion. Once again, as before, I would ask your attention

to the dependence of the digestibility of food in a very high degree—a healthy condition of the digestive tract being presumed—upon its penetrability by the digestive fluids. Fats, which we so willingly abuse as indigestible, are decidedly not so. They are easily absorbed, and even a certain degree of rancidity is, as we have seen, rather favourable than otherwise. Naturally they must not be eaten in excess, as in that case all, even the best Swiss milk, is indigestible, that is, causes mechanical changes, or cannot be absorbed before the whole becomes decomposed, and gives rise to the necessary consequences. The great rôle which the goodness of the food, its preparation, its composition, the rapidity of eating and many other things, play in digestion, I dare not enter upon farther. These things belong to dietetics or metabolism. In this place we can only deal with the general principles which are determined in the digestion of the great groups, and submit some considerations as to their employment in particular cases. It will be better to take the different groups *seriatim*, and for simplicity we will regard milk apart from "drinks."

1. *Drinks.* These consist of watery or alcoholic solutions of salts, organic matter, acids and gases, and are probably completely and rapidly absorbed in the stomach. In dilatation of the stomach they may remain there an abnormally long time, and then perhaps they undergo decomposition. Thence arises the feeling of fluctuation which we so frequently find on palpating dilated stomachs, and the beneficent results of washing out the stomach in such cases, a practice which is still too little familiarised.

2. *Ordinary albumen.* This in the dissolved condition is probably for the most part converted into peptone in the stomach. If coagulated, it requires a longer time, until the walls of the masticated fragments are dissolved by the operation of the gastric juice. Uffelmann saw the edges of such pieces unchanged after two hours, and the aspect externally under the microscope was that of a finely granular

mass. Blondlot found that a dog with a gastric fistula digested 100 grms. of albumen whipped to froth in 3½ hours, and 100 grms. of cooked albumen in 5 hours. We ordinarily regard eggs as pure albumen, and forget the not unimportant yelk contents of fat and salts, the former of which does not become absorbed in the stomach. Yelk of egg is nothing more than an emulsion of fat in solution of albumen, which, according to Prout, contains 17 p.c. of albumen, 29 p.c. fat, and 54 p.c. water. The eggs of the cayman of the Orinoco are used, as Sachs relates, for making oil.

3. *Albumen and fat as milk.* The process of the coagulation of milk in acid gastric juice begins almost immediately after its introduction. It is at first slight, and increases in the first half-hour to its maximum. Casein and fat are gradually separated in more or less compact flocculi or lumps, which are at first sparingly suspended in a milky fluid, but after a short time become more numerous and larger. Therewith the complete separation takes place into curds (fat and casein) and whey (salts, lactose and water). The last is again absorbed in the stomach. The coagulum consists of closely aggregated fat globules imbedded in an amorphous mass, together with other constituents of the stomach, casein, starch granules, muscular fibres, surrounded by coagula which frequently are covered by mucus. Casein-peptone is formed partly in the stomach, partly in the intestine, and absorption of this and of the fat occurs. The so-called milk detritus, which is so often found in the shape of yellowish-white flocculi in the stools of healthy infants, consists, according to Wegscheider, far more of fat, and indeed of olein, palmatin, stearin and a little peptone, than of unchanged albumen. On the other hand, it is certain that, under pathological conditions of the digestive tract, much unchanged casein, syntonin and other albuminoids is excreted. Closer investigations are still needed respecting these very important conditions.

4. *Albumen in the form of meat.* It is to be noticed that the muscular fibrillæ are surrounded by the fibrous perimysium, and the muscular bundles by tendon and fascia. The gastric juice cannot get at the albumen-containing fibrillæ until these coverings are removed, ruptured or dissolved. This happens as they are converted into gelatine, and is dependent upon the resistance of the fibres. These are harder in old flesh than in young, and stronger in raw than in cooked meat. By maceration in hot water the connective tissue is softened and removed. The post-mortem action of acids acts in a similar manner, and we promote this by hanging meat. The muscle-glycogen is changed into lactose, and the connective tissue is loosened by the resulting acid. Raw meat is on this account less easily digestible than cooked meat. But what we lose on one side we gain on the other, as the albumen of the fibrillæ is not coagulated, and so is easily peptonised. By cutting up the meat we endeavour to make the connective tissue as small as possible; and in fact many ill-nourished children and dyspeptic adults digest raw meat better than cooked. In this respect the so-called steamed meat and underdone roast meat preserve the proper medium. We have discussed already the further transformations of the primitive muscular bundles under the head of gastric digestion. The soluble constituents of meat, such as creatin, creatinin, extractives, salts, &c., are, so far as they are soluble in acid solutions, absorbed in the stomach, the principal part passing as chyme with the loosened and softened, but not destroyed, fragments into the small intestine, and then absorbed or transferred to the large intestine, and eventually excreted. The same happens to the fats which are eaten, partly in meat, partly in the accompanying ingredients.

5. *Fat and fatty acids.* These are not absorbed in the stomach and commencement of the duodenum on account of the excessively acid reaction. In whatever form they are ingested, whether alone, whether in combination with other

nutriment, whether contained in the latter, they are always separated from the other constituents and remain intact until acted upon by the bile and pancreatic juice. We have already discussed the details of the process of absorption. But we may add that, according to Ludwig's investigations (Zawilsky), the passage of fat into the lacteals after a copious meal increases up to the fifth hour after taking food, and remains at the same height to the twentieth hour, then sinks to the thirtieth hour, and about this time ceases with the disappearance of the ingested fat from the intestinal canal. Animal fats are more easily emulsified than vegetable fats, and Gad has proved, in his experiments already described to you, that castor-oil, under the conditions of his experiments, generally formed no emulsion. A not insignificant quantity of fat passes into the fæces, partly as free fatty acids, partly as soap, but a part at present still escapes our observation. Zawilsky found, by simultaneous examination of the gastro-intestinal contents, the chyle and the blood, after ingestion of fat, that more fat always disappeared from the intestine than could be found in the chyle and blood. The quantity of fat in the chyle in 22 hours = 84.1 grms., while during this time 132.0 grms. disappeared from the intestine, and other experiments make it extremely probable that this deficit passed somehow directly into the blood. It disappears again tolerably quickly from the blood, as thirty hours after a copious ingestion of fat the blood had regained its normal amount of fat. What becomes of the glycerin derived from the fat, whether it is directly taken up as such, for which the fact of the increase of the liver glycogen after ingestion of glycerin says something, or whether it is decomposed, is unknown.

6. *Vegetables.* Fruits and pot-herbs: we obtain principally from these our necessary hydrocarbons, and to a less extent albuminates. Only the most wretched pauperism or the eccentricity of the vegetarian allows a vegetable diet to suffice; but as we do not live, like savages, on meat alone, the

civilisation of the world is bound up with the knowledge of agriculture. But for the assimilation of the protein substances contained in them, the hydrocarbons, organic acids and salts, there is the difficulty that most vegetables are covered by an envelope of cellulose not easily penetrated by the digestive juices, and carry a ballast of woody cells, epidermis, chlorophyll and other pigments, which in part only undergo absorption. The more, by preparation, boiling, baking, preserving and the like, we make the cell contents, the digestible matter, capable of being affected by the digestive juices, the more easily can the hydrocarbons, the sugar and gum, form absorbable solutions, and the proteids, principally casein from altered legumin, be transformed into peptones. Therefore raw pot-herbs, such as salads, are almost entirely unassimilable, and are excreted nearly unchanged. The digestibility of cooked pot-herbs depends on this. Fruits and legumes are digestible in proportion as in cooking the cellulose is loosened, softened, and the cell contents made accessible. Vegetables possess a nitrogenous constituent, legumin, which is a body resembling casein in all important properties, and gluten, which is very like syntonin, into which plant fibrin and plant gelatine become transformed. This albuminoid becomes in part directly dissolved, in part changed into peptone and so absorbed. Among hydrocarbons we must mention the different kinds of starch and sugar, namely, amylum, dextrin, achroödextrin, inulin, sorbite, &c.; pectin material, gums and vegetable mucus, especially present in pith, fleshy fruits and roots, which are changed into grape sugar, partly in the stomach, partly in the small intestine, but part of which, namely, the pectin and mucus, remain unchanged; whilst the relations of a third group, to which inulin, gums, inosite and sorbite belong, are not yet made certain. I have already described how these hydrocarbons undergo further decomposition by fermentation, and what products are formed from them. Finally, we must add the almost overlooked series of organic

compounds which, in part directly as vegetables, in part as mediate derivatives of them, serve partly as nutriment, partly as gratification, partly as medicine. They all, as well as the inorganic salts, come under observation only so far as they are soluble, or are decomposed into soluble compounds, or can form such. Their absorption occurs chiefly in the upper part of the intestinal tract, and they are of no further interest to us in the study of digestion.

There arises another trivial, but still important question in practice, How often and at what times should we take food?

Between the extremes of the carnivora, which feed once in twenty-four hours or even longer, and the herbivora, which never have done with the business of feeding, man holds a middle place, but not without permitting the recognition in the course of his life of a sort of transition from the herbivore to the carnivore. Infants should have the breast during the first three weeks as often as they wake; after that, every two hours to the third month; then, up to the dentition, every three hours; and later there should be five meals in the twenty-four hours. The last is also true for adults, provided that the principal and secondary meals alternate regularly. Still the intervals between different meals are often too long, between others too short. It is so partially with us, but especially in England and America, where the custom is to eat a large breakfast and then to go till evening without eating hardly anything, and at six o'clock to take another meal, naturally then in abnormal quantity. This not only causes inactivity of body and mind, which always accompanies the digestion of large meals, but is the cause of numerous disorders of the digestive system, especially the stomach. Chronic gastritis, dyspepsia, atony of the mucous membrane, dilatation of the stomach, result from the excessive irritation of the organs. But while the disproportional filling of the stomach after a long pause is injurious and irrational, on the other hand our digestive organs are quite capable of receiving moderate quantities of food and digesting them within a

given time. Feeding, if very prolonged, or only interrupted by short intervals, as in herbivores and infants, would be an unnecessary waste of labour and time. Under certain pathological conditions and in the convalescence of severe diseases, every patient should in this sense be again an infant or a herbivore. The more often and the less at one time he takes of food, the easier will the enfeebled digestive organs be accommodated. Here the time spent by the physician and the patient in discussing the kind and choice of food will not be lost.

The time of day for meals follows the distinctions of country town and city, so that no stringent rules can be laid down. It depends too much upon custom and social relations. The greatest economy of the day would indisputably be attained if the principal meal were taken in the afternoon somewhere between five and seven, so that there should be four instead of five meals daily. This is physiologically permissible provided there is a light but nutritious midday meal, the lüncheon of the English. Then naturally our so-called "abendbrodt" (supper) loses its substantial character and is limited to something to eat and drink. But there is nothing more irrational than to take a large meal late at night and just before going to bed. I may remind you of the results of Busch's investigations, which show a complete cessation of the digestive function during the night; and this is sufficiently confirmed by the broken sleep, restlessness, nightmares, dreams, bad taste in the mouth, &c., which result from late and heavy meals. Yet these simplest and commonest physiological rules are constantly being transgressed, and an intelligent system of dietetics offers a fruitful field for successful work. The relations between brain and stomach functions are well known, and "inability to sleep at night" originates frequently in a fasting stomach. It is a repeatedly proved experience that sleeplessness after long evening work is cured by taking a little bread, cake or the like, just before going to bed.

So much for these matters which properly fall within the range of dietetics.

Gentlemen, I have now reached my appointed limits. We have traced the digestive process through its various stages, and the action of the apparatus which effects this process has been analysed so far as possible in its different phases, in its structure and its various constituents. We may hope that a not far future will widen the sure field of our knowledge by new and lucid investigations, while we do not seek to conceal that this progressive development, here as elsewhere, will be dangerous to many established, still intact, or already tottering theories.

As we have seen in the course of our discussion, processes go on in our organism which do not harmonise with the limited application of the combustion theory to the processes of retrogressive metamorphosis, and we gain new support day by day for the view that our body not only, as was formerly supposed, breaks up the ingested nutriment and makes use of the products of decomposition as such, but that it builds up out of these new compounds, performed not only by destructive but by synthetic processes; so we see in the limited field of the subject of Digestion a decided revolution against the theories of the schools. The hard and fast lines within which the processes of digestion were included, one might almost say for the sake of a certain utilitarian principle, attractive as they are by a kind of popular comprehensiveness, can be maintained no longer in their full extent.

Quite apart from the fact that we now can discern better the functions of the participating glands, principally the pancreas, according to the kind and energy of their action, we were earlier too much inclined to regard the various digestive factors apart from each other, and to make artificial limits which practically are not present, just as we—especially in considering absorption—are used to ascribe too large a field to the action of physiological forces, and too

small a field to chemical forces. We have seen how the fermentative actions of various digestive juices resemble each other, how the physiological glandular actions and putrefactive processes are allied to one another, how physical and chemical forces are not separated but work in common, and how, as a new factor, the specific forces of the living cell, which we provisionally must admit, although still inexplicable, come into play; in short, how processes take place, in truth, by the co-operation of numerous factors, which sometimes aid and sometimes hinder them, and which are more complicated than we can reproduce with our retorts, dialysers and air-baths, outside the organism; and still the latter is the unavoidable and correct way to trace the more delicate processes of digestion. Such investigations are of great and primary significance. But we must not forget that under all circumstances we need the control of experiments on the living organism whenever we can provide the necessary experimental conditions, or a pathological process gives us the necessary material.

Gentlemen, in this matter all of us may assist, and by a single good pathological observation, such as the latest publication of this kind, Demant's researches on the intestinal juice (p. 103), or my own case of præternatural anus (p. 69), give important aid to scientific medicine. But this requires a survey of the present position of the questions *sub judice*, so that you may follow easily the exposition of such a rapidly growing and advancing department of knowledge as the subject of Digestion now is.

But we owe physiology still more than we can repay. I need not insist again upon the importance of the knowledge of physiological phenomena for the right understanding and treatment of pathological processes. In immediate connection with the experiments of physiologists, in part directly stimulated by them, practitioners have in late years successfully turned these views to account in pathology. Many most excellent clinicists have recently directed their energies

to this department of knowledge. The use of the stomach-pump, nutritive enemata, artificial nutriment and digestive preparations, give eloquent testimony to this. But there is still much to be done, and a large field lies open to our common labour. The best result of our meetings would be if they awaken in you, Gentlemen, a new and lively interest in this important branch of our knowledge.

J. Munk. Ueber die Verbreitung ungeformter Fermente im Thierkörper. Deutsch. med. Wochenschrift, 1876, No. 48.

Kühne. Ueber die Verbreitung einiger Enzyme im Thierkörper. Verhandlung. d. naturhist- med. Verein z. Heidelberg, ii. Hft. 1.

Hüfner. Loc. cit.

Uffelmann. Loc. cit.

Pavy. A Treatise on Food and Dietetics. London, 1875.

W. Roberts. On the Digestive Ferments and the Preparation and Use of artificially digested Food. London, 1880.

APPENDIX.

Page 5. *The experiments proving the presence of ozone in gas* pumped from the blood were performed by me in 1873, but as in the mean time I came to know of Pokrowsky's experiments, they were not published.

Page 10. *The influence of neutral salts in fermentation.* Nasse worked with 4 p.c. solutions of salts, starch and the following ferments, taking great care to perform all the experiments under equal conditions. The intensity of the fermentation is shown in the following table, in which the relative positions of the promoting and retarding salts are shown:

Inverting ferment from yeast.	Saliva.	Pancreatic ferment.	Diastase.
Ammon. sulphate	Sodium chlor.	Potass. nitrate	Amm. sulphate
„ chloride	Amm. „	Sodium chlor.	„ chloride
„ nitrate	Sodium sulph.	Ammon. „	„ *nitrate*
Sodium sulphate	*Potass. nitrate.*	Sodium nitrate	Potass. sulphate
Potass. „	Sodium „	„ sulph.	Sodium „
Sodium nitrate	Potass. sulph.	Potass. chloride	Potass. nitrate
Potass. „	Ammon. „	Ammon. nitrate	Sodium „
Sodium chloride	Potass. chloride	„ sulph.	„ chloride
Potass. „	Ammon. nitrate	Potass. „	Potass. „

For example: saliva acting on starch in a 4 p.c. sodium chloride solution, gives rise to the most rapid and energetic action (transformation of starch into sugar). The action is less strong in a 4 p.c. solution of chloride of ammonium or sulphate of soda; and from nitrate of potash downwards,

there commences a retarding action in the fermentative process. The action of an equal quantity of equally active saliva on an equal quantity of starch gruel, without addition of salts, served as a standard of comparison. This retarding action, for the inverting ferment of yeast, begins with sulphate of soda, with diastase, with nitrate of ammonia; while all the salts under the head of pancreatic ferment promote the action more than pure water. For example, if the action of pancreatic ferment on starch in pure water = 100, in a 4 p.c. solution of nitrate of potash it = 131, and in a solution of sulphate potash it = 107. As the simplest and most direct result of these experiments, which certainly have a practical significance, we may learn, what our instinct has already rightly taught us, to eat salt with dry bread, as in fact we find that the salivary ferment works best in a solution of sodium chloride.

Pages 9 and 61. The persistence of the ferment in presence of high temperatures appears to depend upon the employment of ferments or gland extracts as much as possible free from albumen. At least I have obtained no decided action with extracts which gave much flocculent albumen on heating. But at best the action of the heated extract lasted longer than that not heated, and—in digestion with hydrochloric acid solutions—nearly as long as in a third experiment in which there were only albumen and hydrochloric acid. From subsequent experiments I am still doubtful whether the statement made in the text—otherwise unessential for our purpose—as to the persistence of ferment action by heat, really relates to a true ferment action, or, in the case of pepsin digestion, only to a conversion of native albumen into syntonin by the hydrochloric acid solution.

Page 53. *Examination of some artificial digestive preparations.*

1. Pepsinum germanicum solubile, from Witte, of Ros-

tock, consists of a white amorphous powder, which under the microscope is made up of small lumps and granules. It is not mixed with starch, and gives no reaction with liq. iodi. It dissolves in cold water about 1 : 50, but is insoluble in absolute alcohol. The solution and the powder digest strongly with fibrin and hydrochloric acid, phosphoric acid or lactic acid in proportional concentration. From the watery solution of pepsin we obtain, by boiling and adding acetic acid, no precipitate; with glacial acetic acid and ferrocyanide of potassium, a slight precipitate; and with solution of tannin, a denser cloud. The xanthoprotein reaction and Millon's reagent show slight traces of albumen. The preparation is to be regarded as a relatively pure ferment. 1.0 grm. pepsin, 2.2 grm. fibrin, with 50 ccm. of hydrochloric acid solution, are digested at 40° C. in forty minutes. The clear solution gave, with previous neutralisation, a slight, scarcely visible, precipitate; but a strong peptone reaction with liq. potassæ and copper sulphate, no cloud on heating; a slight cloud with acetic acid and ferro-cyanide of potassium. A great part of the fibrin was also changed into peptone.

2. Ptyalin-pepsin is a grey powder also consisting of numerous lumps and granules, but containing much starch. Liq. iodi colours the starch cells red-violet (reaction of erythrodextrin); treatment with liq. potassæ swells them, they become pale and dissolved. The watery solution is coloured rose-red with liq. potassæ, and gives, when heated with liq. potassæ and copper sulphate, no reduction of copper. The albumen reactions are the same as in pepsinum germanicum solubile.

3. Ptyalinum vegetabile, a reddish-grey powder, consists of starch cells, only without the above-described lumps and granules. This is shown by the microscope as well as when the watery solution is treated with liq. iodi, by giving the erythrodextrin reaction. No starch reaction, no sugar, no albumen.

Both preparations act well, but are inferior to pure pepsin in their action. In a mixture of hydrochloric acid, fibrin,

2 p.c. starch gruel and ptyalin-pepsin, the fibrin becomes partially peptonised and the starch partly converted into sugar. But after five hours' digestion, besides a copious precipitate on neutralisation, as well as with acetic acid and ferro-cyanide of potassium, there is also the starch reaction with iodine.

4. Pancreatin, a greyish-yellow amorphous powder, showing starch cells and the lumps and granules. The same reactions as ptyalin-pepsin. The most lately produced "Pancreatin" by Mr. Witte acts very well on starch and fibrin when treated with soda (see Weitere Beiträge zur Lehre von der Verdauung, by C. A. Ewald. Ztschrft. f. klin. Med. Bd. i. Hft. 3).

In all the experiments the following proportions were employed: ferment, 1.0 grm.; fibrin, 2.5 grm.; hydrochloric acid solution of 0.35 p.c., 500 or 100 ccm.; and starch gruel of 2 p.c. Temp. = 40°.

5. Peptonum siccum is a brownish-yellow powder, which, when dissolved in two parts of water, gives peptonum solubile (Adamkiewicz's peptone). It consists of a thick brownish syrup. I have dissolved 8.4 grms. of dry peptone in 50 ccm. of water at 38°, and obtained a clear golden yellow solution of very feebly alkaline or almost neutral reaction. It gives no precipitate on boiling, but does so on acidulating with acetic acid. A slight cloudiness occurs on previous neutralisation or acidulating very feebly with hydrochloric acid. With acetic acid and ferro-cyanide of potassium, with tannin in acid solution, with acetic acid and chloride of sodium, with nitric acid, a copious precipitate occurs. With liq. potassæ and copper sulphate, a beautiful, somewhat too violet, peptone reaction. This preparation closely corresponds, as Adamkiewicz states, to the body described by him as peptone.

But if by means of excess of hydrochloric acid, or any other of the above methods, we have obtained a copious thick precipitate which dissolves with heat, separates again

in the cold, and precipitate and fluid be submitted anew to the hydrochloric acid pepsin digestion with active pepsin (I used Witte's pepsinum germanicum), after some time the entire precipitate becomes dissolved to a quite small residue. This clear wine yellow filtrate gives a very strong reaction with copper sulphate and liq. potassæ, no precipitate with heat, nor with chloride of sodium and dilute acetic acid, or glacial acetic acid, nitrate or hydrochloric acids, or previous neutralisation with dilute soda lotion and with excess of the same. A slight cloud follows treating it with acetic acid and ferro-cyanide of potassium, a denser one with hydrochloric acid and tannin. The latter dissolves with heat; the former becomes denser, not from the separation of albumen, but because ferro-cyanide of potassium, heated in solution of acetic or hydrochloric acid, gives a copious precipitate. We see that on further digestion the fluid containing Adamkiewicz's peptone corresponds in its reactions (with the exception of the slight cloud on treatment with acetic acid and potassium ferro-cyanide) very closely to the characteristic reactions of peptone solutions, and has lost part of its former characters. If we would regard peptone, as was formerly customary, as the final product obtained by the action of pepsin on acid solutions, we must look upon Adamkiewicz's product as an unfulfilled product of the digestion of albumen.

In addition, I have examined the following preparations, from Simon, of Berlin:

1. Pepsinum pulverisatum. A snow-white powdered preparation, easily soluble in water. The solution does not coagulate on heating, gives no precipitate with acetic acid and potassium ferro-cyanide, nor with hydrochloric acid and tannin. No peptone reaction with liq. potassæ and copper sulphate; no starch reaction with liq. iodi. Microscopically it consists of large and small amorphous lumps. Pepsin, 0.5 grms. + fibrin, 2.5 grms. + hydrochloric acid solution, 0.3 p.c. 115 ccm., dissolves in the first hour of digestion to a few flocculi, which do not disappear in the seventh and

eighth hour. The solution is whitish, slightly turbid. On neutralisation there is a moderate precipitation of syntonin. The filtered solution does not coagulate on heating, or after acidulating with acetic acid. Slight precipitate with acetic acid and potassium ferro-cyanide.

A double experiment of equal digestive mixtures with this pepsin and Witte's pepsinum germanicum solubile (pepsin, 0.5 grm.; hydrochloric acid solution, 115 ccm.; fibrin, 2.5 grms.), showed that the fibrin in both cases was dissolved with equal rapidity.

2. Pepsinum granulatum. Brown granules from the size of a pin's head to a lentil. Little soluble in cold water, in which, after a time, it forms a turbid yellow fluid. Slight precipitate on heating and acidulation with dilute acetic acid. Very copious precipitate on addition of acetic acid and potassium ferro-cyanide, hydrochloric acid and tannin. The turbid solution is cleared by caustic potash and gives a strong peptone reaction. The preparation is rendered impure by much albumen and peptone. Its digestive power is much feebler than that of the powdered preparation. The digested solution is thick, gives a dense precipitate on neutralisation, feeble peptone reaction, copious albumen reaction, but no precipitate after heating and acidulation.

3. A so-called "pancreatin." In external appearance and reactions, very like the preceding, but rather finer grained. Pancreatin, 0.5 grm. + soda solution of 1 p.c. 115 ccm. + fibrin, 2.5 grms., did not digest. The fibrin after six hours lay shrunken together and undissolved at the bottom of the glass. The supernatant fluid gave a strong reaction of albumen, but none of peptone. A control experiment with the same quantities of soda solution and fibrin, and 10 ccm. of glycerine extract of pancreas, was completely dissolved to a few flocculi at the end of two hours.

The result of these experiments is to show that Witte's and Simon's white pepsin powder—pepsinum germanicum solubile of Witte, and pepsinum pulverisatum of Simon

—possess the best action of all the preparations tested, and may be considered equally good. Ptyalin-pepsin and pepsinum granulatum are less active. Ptyalinum vegetabile is distinctly inferior, in regard to the rapidity of its action, to pure mixed saliva or pancreatic juice. The so-called pancreatin of Simon is quite unable to act on albumen. Besides, if the latter did possess digestive properties—and I have tested an English preparation, from Messrs. Savory and Moore, which dissolved fibrin in alkaline solution, so that the resulting solution showed the customary peptone reactions—*yet for therapeutic purposes, so far as concerns administration by the mouth, pancreatin preparations are quite worthless.* Kühne has recorded that the pancreatic ferment isolated by him which digests albumen, trypsin, when brought in contact with gastric juice or pepsin in acid solution, is digested like any other albuminoid, and its action was destroyed. We may convince ourselves of this fact without using pure "trypsin," by the aid of an active glycerine pancreatic extract, in the following manner. Fibrin, 7.5 grms. + hydrochloric acid solution of 0.3 p.c. 300 ccm. + Witte's pepsin, 0.5 grm. + glycerine pancreatic extract, 10 ccm., is allowed to digest, and will be dissolved in one hour. The pepsin action is most complete. Now if it be neutralised with soda, the very slight precipitate of syntonin removed, and the filtrate treated with concentrated soda solution till it contains about 1.5 p.c. of soda, then 5 grms. of fibrin added, the action of the glycerine pancreatic extract is free to manifest itself. But the fibrin remains quite undissolved, whilst equal quantities of fresh glycerine extract, fibrin and soda solution, are digested in a short time.

The power of digesting albumen in the pancreatic ferment is destroyed by the action of the gastric digestion. But, apart from its introduction by the rectum, we cannot bring pancreatin to the place where its own action could be exerted, without subjecting it previously to the destructive influence of the gastric juice. Only in the quite rare cases in which the

gastric digestion is quite at a standstill, or the alkalinity of the gastric contents favours the commencement of an artificial pancreatic digestion in the stomach, would the administration of active pancreatic preparations have a rational basis. How far the English preparation examined by me may be employed as a constituent of meat pancreas enemata, is a matter I am now investigating, and I must postpone further remarks on this point. I have also examined the so-called Ergesser's powdered pancreas, made by Mr. Keller of Freiburg. The results are detailed in my paper referred to above (see Weitere Beiträge, &c.). I am glad to find that Dr. Roberts, in his Lumleian Lectures for 1880, confirms the view I have expressed as to the action of pepsin on trypsin.

Page 60. *Table of Gastric Digestion.*

Food, arranged according to the time required for digestion in the stomach.	Mode of preparation	Duration in stomach till solution or disappearance.	
		Beaumont.	Richet.
Schnaps	....	....	30′ to 40′
Milk	....	....	30′, 1 h
Cauliflower	....	....	
Cane sugar...............	....	....	
Bullocks' tripe	roasted	1 h	
Pigs' feet	boiled	1 h	
Rice	"	1 h	
Peas with butter	....	....	1—2 h 30′
Baked potatoes	....	....	1 h, 2 h 15′, 2 h 30′, 3 h
Whipped eggs	raw	1 h 30′	
Barley broth	boiled	1 h 30′	
Salmon trout...........	"	1 h 30′	
Ripe apple...............	raw	1 h 30′	
Meat (?)	....	....	1 h 30′, 2 h 30′, 4 h, 5 h 30′
Venison	boiled	1 h 45′	
Calves' brains	"	1 h 45′	
Sago	"	1 h 45′	
Spinach	"	....	1 h 45′, 2 h, 4 h

Food, arranged according to the time required for digestion in the stomach.	Mode of preparation	Duration in stomach till solution or disappearance.	
		Beaumont.	Richet.
Maccaroni with fat ...	boiled	....	1 h 45′, 2 h 30′, 3 h 15
Eggs	raw	2 h	
Milk	„	2 h	
Bread	baked	2 h	
Salad	raw	2 h	
Soup with fat and bread	boiled	....	2 h
Rice with fat	„	....	2 h, 2 h 45′, 3 h, 3 h 15′
Lentils with egg	„	....	2 h, 2 h 45′
Bullocks' liver	raw	2 h 15′	
Turkey	roasted	2 h 25′	
Pork	boiled	2 h 30′	
Lamb	„	2 h 30′	
Beans	„	2 h 30′	2 h
Potatoes	„	2 h 30′	2 h 30′
Cabbage	„	2 h 30′	
Cauliflower with fat ...	„	....	2 h 30′, 2 h 45′
Rice with fat and wine	„	....	2 h 30′
Maccaroni with fat ...	„	....	2 h 30′, 3 h 45′
Oysters	raw	3 h	
Mutton	stewed	3 h	
Soft eggs	boiled	3 h	
Beef-steak	....	3 h	
Ham	boiled	3 h	
Lean bacon	fried	3 h	
White bread	baked	3 h	
Fish	boiled	3 h	
Onion soup	„	....	3 h
Eggs with sugar	....	....	3 h 30′
Pork	roasted	4 h	
Poultry	„	4 h	
Veal and bacon	„	4 h	
Black bread	baked	4 h	
Cartilage	boiled	4 h	
Cabbage	„	5 h	
Pork	salted	5 h	
Hard eggs	boiled	5 h	

The statements in these tables are derived from two cases of gastric fistula. The first is the famous Canadian, St. Martin (observed by Dr. Beaumont), who had a fistula in consequence of a gun-shot wound. The second had an impermeable stricture of the œsophagus, resulting from cicatricial contraction after swallowing caustic potash. He was gastrotomised by Verneuil and afterwards observed by Richet. He obtained food by its being injected through the fistula. The statements in the cases recorded by Schröder, Grunewald, Kretschy and Uffelmann, are too little exact to be included in this table. Naturally, such observations give only approximate data. We can easily see from Richet's statements, where one and the same article of food was repeatedly digested, how different may be the period of its duration in the stomach; but we know also how much the gastric digestion is dependent upon general conditions, physical influences, &c. Richet justly remarks: "Nul organe, peut-être, n'est aussi fantasque dans sa fonction que l'estomac."

Page 56. *The thermo-electric determination of the temperature of the stomach* was performed by me in Frerichs' clinic in the summer of 1876, principally with the view of ascertaining the relations of peripheral and central body temperature in great falls of temperature effected by salicylic acid. A provisional note resulted in the shape of an article "On Salicylic Acid as an Antipyretic," in the Practitioner for 1877. This is not the place to describe in detail this experiment, which, so soon as I obtain the necessary clinical material, will be published. The following may be sufficient to support the statements in the text. In healthy persons with empty stomachs, the stomach temperature is generally higher than that of the axilla, averaging in ten experiments 0.6° C. But if the patient breathes forcibly, even when the mouth is shut and respiration is by the nose only, decided variations occur, which may reduce the gastric temperature to 0.3° below the axillary temperature (the average of four experiments). These

variations ceased when the patient breathed steam at 40°. The result of the salicylic acid experiments (three series of experiments) showed that in two instances the stomach temperature sank proportionately to the peripheral temperature; in the third, indeed, it sank to 1.2° C below the axillary temperature. This and other experiments—for example, on the rapidity of warming or cooling of food in the stomach—are still not sufficiently numerous. The facts related in the text, however, were regularly noticed, and the thin wire sound, covered with india-rubber tubing, used by me, could scarcely have caused a mechanical distension of the œsophagus.

Page 65. *The method of washing out the stomach.* The always unacceptable occurrence of tearing the mucous membrane by the stomach-pump and the usually quite unnecessarily sharp-edged fenestra of the œsophagus-tube, cannot occur if we observe the method first described by me,* of emptying the stomach by an ordinary long piece of gas-tubing. We can introduce one end of such a well-oiled tube without any difficulty, especially if the pharynx of the patient has been previously slightly anæsthetised by painting with ether, chloroform or borax lotion. To the free end of the tube a funnel is attached; the stomach and tube filled; then by lowering the funnel whilst compressing the tube just below it, the syphon action takes place. It scarcely needs to be said that if we leave the U-shaped tube hanging from the mouth when the stomach is full, the surface of the water in the funnel corresponds to the height of the water in the stomach or œsophagus, and that instead of a funnel we can connect a stomach-pump to the tube. With this plan I have never happened to tear off pieces of the mucous membrane or to cause hæmorrhage. Any one must manipulate very clumsily to wound the mucous membrane with this soft tube, and even in strong suction, whether from syphon or pump

* In the Lancet for June 4th, 1879, Dr. Alderson says the stomach syphon was first described by Dr. Arnott in 1829.

action, the walls of the tube lie too far apart for any tearing of the mucous membrane to take place. It is wonderful, in our scribbling times, how difficult it is for this simple practice to make its way. Thus in an article by Haenisch, "die Verletzungen der Magenschleim haut durch Magenpumpen"* (Deutsch. Archiv. f. klin. Med. Bd. xxiii. p. 579), I find no mention of my method; but, on the contrary, I read that, by using an ordinary œsophagus-tube, a piece of mucous membrane 3.4 cm. long was torn off!

Page 65. *On the question of the origin of gastric ulcer.* Koch and I made six experiments on artificial lowering of blood-pressure by section of the cord, and two in which the lowering of blood-pressure was effected by copious venesection without section of the cord. The former animals had their cords divided at the height of the fourth cervical or second dorsal vertebra, and the animals after the operation were covered up warmly or put into a warm chamber with an inside temperature of 30° C. In the first experiment, at the same time the duodenum at the pylorus and some of the branches of art. gastro-epiploica dextra going to the stomach, were tied. The animals were fed in the morning of the experiment with bread and meat, but then, with the exception of experiment IV., no more food, but every day 50 to 100 ccm. of hydrochloric acid solution were administered by the œsophagus-tube. All the animals were dead in the course of sixty hours, that is, they either died as a result of the operation, or were killed, as in the case of the dog rendered anæmic by venesection, and that in experiment I. Only one dog with section of the spinal cord lived ten days (experiment IV.). The anæmic dog had scarcely any changes in his stomach. All the animals [illegible] divided cords had typical gastric, and some duodenal ulcers, if they lived longer than thirty-six hours after the operation. But these were only three out of the six dogs. In these cases

* Wounds of the Gastric Mucous Membrane by the Stomach-pump.

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the changes were quite characteristic, as shown in the following note from experiment IV.:

A middle-sized poodle. On the 17th July, 1878, section of the cervical cord at the level of the seventh vertebra. After the operation, complete paralysis of the lower extremities. The animal is so lively that it crawls about the room by its fore-legs, barks, &c. 50 ccm. of hydrochloric acid solution, 2 p.c., daily. Eats well. This state continued till July 25th. The dog then became sickly, ate no more, and died on the 28th July. The temperature was normal to the 27th. AUTOPSY: *stomach contents:* a little thick, brownish red mucus; shows only reddish brown detritus, sometimes aggregated in heaps, sometimes in lumps and punctiform. No muscular fibres, crystals, starch, sarcinæ, vibrios or other fungi. The stomach contents mixed with a little water and filtered *did not digest fibrin. Mucous membrane:* pale, anæmic. From the cardia especially in the fundus, covered with numerous superficial losses of substance, the size of a pin's-head to a millet-seed, generally round, though sometimes oval or irregularly notched. These were bounded by a thin border of whitish, apparently intact, mucous membrane, sharply contrasting with its surroundings, so that the whole had some resemblance to herpes circinnatus. In the proper ulcers the outer ring was more diffuse. The former were often covered with brownish red, easily removable mucus. Only in a few places did the ulceration reach the muscular coat. These ulcers were always at the apices of the folds or on their sides, never at the bottom. About 3 ccm. above the pylorus they were increased in size, especially upon a transversely running fold, when they were deeper, and covered with a dark, blackish brown adherent scab. The largest ulcer, close to the pylorus, was 1.7 cm. long. The duodenum was much injected, the mucous membrane everywhere loosened. Just below the pylorus were two shallow ulcers the size of peas, similar to those in the stomach. The serous coat of the stomach and intestine was normal. Otherwise nothing par-

ticular. Section of cord complete. *Microscopically*, thin sections at right angles to the surface of the stomach, hardened in bichromate of potash and alcohol, showed that the gland tubules in the bloodless ulcers towards the submucosa were corroded away (digested?), without there being any pus corpuscles, fresh connective tissue corpuscles, or other evidence of an inflammatory process. The dark brown scabs already referred to were formed by the blood on the hæmorrhagic ulcers, which was poured out on the floor of cup-shaped ulcers, and lay between the gland tubules and in the submucous tissue. Their origin from a (corroded?) vessel of the submucosa was very visible in some places. In the deepest places the tubules were quite destroyed; between masses of detritus, blood corpuscles and remains of intertubular tissue, lay some well-preserved gland cells. In other places the vessels must either have been opened as the ulcer penetrated the mucosa, or the hæmorrhage must have originated in the intertubular vessels which we saw in such places still covering a remnant of the fundus of the tubules in the submucosa in the entire extent of the ulcer, whilst the bleeding vessel appeared to lie under them in the submucosa. We noted quite analogous appearances in the other two above-named cases. In a quite healthy dog, which for four weeks had daily 50 ccm. of hydrochloric acid solution of 2 p.c., without any result appearing, on the 18th to the 20th August on each occasion about a quarter of the entire blood was drawn from a vein. The dog collapsed and died on August 21st. On dissection, we found the gastric mucous membrane as if tanned; the stomach small, pale and contracted. On a white, bare-looking, connective tissue-like ground were numerous pale red prominences which resembled urticaria. They were, as shown by microscopical examination, the remains of the proper gland substance. Here a more diffuse superficial corrosion was caused by the hydrochloric acid, but no proper ulceration resulted, and obviously it was the chronic excess of acid fluid, so far beyond the physiological proportion, that brought about this change.

Page 76. *Rutherford, Vignal and Dodds,* give the following table of the effects of different drugs in the secretion of bile on fasting animals in whom biliary fistulæ were formed :

Name of the drug.	Dose in grms. per kilo of body weight.	Bile secretion per hour and body weight.	
		Before.	After.
Curare in small doses causes in the first 4—5 hours a uniform secretion which gradually diminishes		0.35 0.25 0.15	
Podophyllin	0.9	0.04	0.47
"	0.23*	0.52	1.01
Aloes	6.9	0.34	0.69
"	12.0	0.26	0.93
Rhubarb	3.06	0.17	0.32
Colchicum	2.5	0.13	0.45
Euonymin	0.26*	0.25	0.47
"	0.21*	0.07	0.46
Ipecacuanha	2.2*	0.24	0.55
"	0.49*	0.18	0.38
Colocynth	0.53*	0.20	0.45
"	0.4*	0.16	0.27
Jalap	1.2*	0.16	0.29
Sodium sulphate	32.3*	0.25	0.38
Potassium sulphate	10.7	0.31	0.47
Cream of Tartar	37.0	0.23	0.33
Corrosive sublimate	0.0077*	0.17	0.47
" "	0.0071*	0.20	0.55
Corrosive sublimate Calomel	0.005 0.101	0.48	0.72
Corrosive sublimate Calomel	0.0027 0.054	0.22	0.85
Sodium benzoate	1.320	0.22	0.64
Ammonium benzoate	0.737	0.24	0.54
Sodium salicylate	1.00	0.17	0.56
" "	1.55	0.26	0.66
" "	2.15	0.32	0.89

* These drugs were dissolved in bile instead of being injected in watery solution.

I have omitted some rare alkaloids from the table, although some, as, for example, iridin, sanguinarin, physostigmin, juglandin, exert a marked influence in increasing the biliary secretion. The most striking is the great increase of the secretion after podophyllin, corrosive sublimate and sodium salicylate. Tannin, pilocarpine, morphia, hyoscyamin and alcohol, appear to have no particular effect on the secretion of bile. According to Röhrig, croton oil is only a very feeble bile stimulant. According to the latter observer, colocynth, jalap, aloes and rhubarb, act sharply, and, agreeably to Rutherford's statements, lead to the secretion of a thick turbid bile.

After diabetic puncture, Naunyn has observed slowing of the bile secretion.

Page 102. *Treatment of diarrhœa with cold-water enemata.* Those forms of diarrhœa, especially in children, which depend chiefly upon changes in the large intestine, I have treated for about a year with injections of cold spring water and indifferent medicine (hydrochloric acid or soda). After each motion, the child has an enema of 200—300 ccm. of cold water, which by slight abdominal pressure is expelled again. Then about 50 ccm. are injected which should be retained. The results are surprisingly good, and the mothers take to this treatment more easily than one would think. In adults I have had only two opportunities for this treatment, but both times with good results. In the latter cases, naturally, many external circumstances oppose the method. Messemer (Cold-water Enemata, American Journal of the Medical Sciences, July, 1878) has found the method a very good one. Whether, as he believes, it acts by washing away irritating substances, or, as I think, by diminishing peristalsis, remains uncertain. Still it has one great advantage for poor practice: *it costs nothing.* I have treated a large number of cases by this method in my polyclinie, but can give no definite statistics.